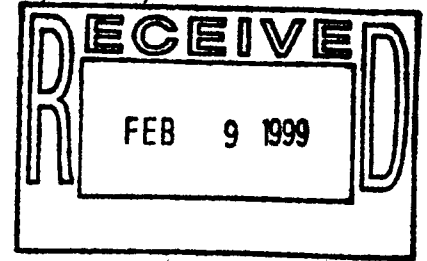


**Littlewood & Fennell, P.A.**

**Independent Public & Health Policy Research, 4103 Lullwood Road, Austin, TX 78722**

February 8, 1999

Dr. Larry Hart  
National Toxicology Program (NIEHS)  
111 T.W. Alexander Drive, Building 101, South Campus  
Research Triangle Park, NC 27709-2233



Dr. Hart,

Enclosed are our public comments on the National Toxicology Program's decision to list environmental tobacco smoke (ETS) as a Class A carcinogen.

We find NO convincing evidence that ETS should be so listed. We do find convincing evidence of statistical manipulation, misrepresentation of data and, as Lewis Carroll so charmingly put it "having the verdict before the trial."

We have no affiliation with either industry or government. Indeed, this was a labor of our love for sound science and intelligent public health policy. Specifically:

We own no stock or stock options or other financial instruments  
of companies whose products are discussed in these comments,

Have not been paid consultants with either industry or government  
in this matter,

Have not been employed by either industry or government in this  
matter,

Have received no fee or honorarium for these comments, nor for  
conducting research related to this material,

Have received no speakers fees or educational grants or travel  
assistance from industry or government regarding this matter.

Considering the thinly veiled contempt expressed by members of the subcommittee, we felt it quite important to make these points.

Sincerely,

Anne Fennell

Encl. Comments on listing ETS as a carcinogen, "No convincing evidence. . ." 63 pages.



**Environmental Tobacco Smoke**

**NO CONVINCING EVIDENCE  
OF CARCINOGENICITY**

Public Comments solicited in response  
to the  
National Toxicology Program  
Board of Scientific Counselors on Carcinogens Subcommittee  
regarding listing of environmental tobacco smoke  
as a human carcinogen.

February 8, 1999

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Austin, TX 78722



Environmental Tobacco Smoke  
NO CONVINCING EVIDENCE OF CARCINOGENICITY

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# **Environmental Tobacco Smoke has NOT been proven to be a human carcinogen.**

## **SUMMARY**

Environmental tobacco smoke (ETS) has NOT been proven to be a human carcinogen.

## **Background**

We have thoroughly reviewed the materials supplied to us by the Environmental Toxicology and National Toxicology Programs, National Institute of Environmental Health Sciences. In addition we have acquired complete studies, abstracts, oral presentations and other documents related to the conjecture that environmental tobacco smoke is a possible human carcinogen.

## **Observations**

We have assessed the material according to the criteria set forth by Bradford Hill<sup>1</sup>, using a re-organization suggested by Mengersen *et al.*<sup>2</sup> Overall, more than 75 percent of epidemiologic studies fail to link secondhand smoke to cancer. The remaining studies rely on weak statistical associations. Of those that suggest association, none reliably confirm exposure data or adequately control for major confounding risk factors. There are substantial problems with publication bias, misrepresentation of relative risks, and unacceptable epidemiologic methodology. Animal studies did not use ETS or any acceptable surrogate and were limited to a single animal model. Other studies that found no association between ETS and cancer were apparently ignored. There appears to have been an ongoing and systematic effort on the part of the USEPA, CEPA and NIH, as well as those involved with this listing process to discount credible presentations and ignore studies inimical to a balanced scientific risk assessment of ETS in favor of subjective standards of evaluation that accord with preconceived opinion.

## **Recommendation**

We recommend that the National Toxicology Program NOT include environmental tobacco smoke among its list of carcinogens.

We strongly recommend: 1) that future decisions rely upon accepted and *accurate* representations of relative risks, 2) a substantial effort be made to identify and assess both published and unpublished studies showing negative correlations, 3) that the possibility of ETS hormesis be considered in light of the fact that a significant number of the studies included in the referenced background material indicate a potential protective effect for ETS, 4) that two-tailed analysis with a 95% confidence intervals be consistently applied to account for the high number of negative correlations, and 5) that raw data from all studies be made available for resampling by a variety of methods.

We further recommend that a panel of *objective* specialists be convened -- with no prior advocacy affiliations and with no vested interests in or bias toward a positive conclusion.

## **Environmental Tobacco Smoke:**

# **There is NO convincing argument for human carcinogenicity.**

---

A substance is categorized as a Group A Human Carcinogen "only when there is sufficient evidence from epidemiologic studies to support a causal association between exposure to agents and cancer."<sup>3</sup>

In addition, three criteria must be met before a causal association can be inferred between exposure and cancer in humans:

1. There is no identified bias that could explain the association.
2. The possibility of confounding has been considered and ruled out as explaining the association.
3. The association is unlikely to be due to chance.<sup>4</sup>

Using these guidelines as a basic standard, we find that Environmental Tobacco Smoke (ETS) has *not* been convincingly shown to be a human carcinogen.

### **Key Messages**

There is no convincing scientific evidence -- either epidemiologic or biologic -- that ETS is a human carcinogen.

There has been and continues to be a persistent and disturbing pattern of reaching conclusions prior to rigorous scientific investigation.

There has been and continues to be a pattern of 'data torturing' and scientific distortion to force an unwarranted conclusion.

There has and continues to be a lack of neutrality in the formation of supposedly 'independent' scientific advisory boards convened to assess risks (or lack thereof) associated with ETS.

In short, we are appalled at the misrepresentation of data, willful omission of data and bias clearly displayed by the NTP subcommittee for listing ETS as a human carcinogen.



## 1. OVERVIEW OF BACKGROUND MATERIAL

We were supplied with background material (two volumes titled "Report on Carcinogens, Background Document for Environmental Tobacco Smoke," dated December 2-3, 1998, from the meeting of the NTP Board of Scientific Counselors, Report on Carcinogens Subcommittee). In addition, we received the transcript on Environmental Tobacco Smoke from the NTP Board of Scientific Counselors Report on Carcinogens Subcommittee meeting that was held on December 2-3, 1998.

For the sake of clarity, we refer to this material as:

Volume I (larger volume, no volume specific page numbers)  
Volume II (smaller, 95pp document).  
Transcript (pp 169-234)

**Volume I:** Material in Volume I was limited to three sources.

1. Vol. 38, of IARC's 1986 Evaluation of the carcinogenic risk of chemicals to humans.
2. USEPA's 1992 report on the respiratory health effects of passive smoking.
3. California EPA's 1997 report on the health effects of exposure to ETS.

This is largely meta-analytic material. The majority (more than 75%) of the studies included show no statistically significant association between ETS and cancer (See Table 1). Several studies should be extensively resampled using the authors' raw data. We have included comments on Brownson and Fonham, two of the larger studies. In total, only by using a reduced confidence interval of 90%, was the USEPA able to find a statistically weak 1.19 relative risk for ETS and lung cancer. In addition, we are concerned at the one-tailed test performed on the material. Many of the studies show a negative correlation for ETS and lung cancer -- implying a protective effect, especially for children. For this reason, a two-tailed test, acknowledging the possibility of ETS hormesis, should have been performed.

**Volume II:** Draft RoC Background Document for ETS

The basis of this material also come from the same USEPA and CEPA sources. It includes animal studies using a single animal model that featured neither actual ETS nor a reasonable surrogate. Our literature search indicates a number of well conducted animal studies which show negative results for ETS and lung cancer.

**Transcript:** This is a verbatim transcript of the Meeting of the National Toxicology Program Board of Scientific Counselors, Report on Carcinogens (RoC) Subcommittee, dated 12/02/98. Where we could, we have reviewed entire studies, comments and abstracts referred to throughout the transcript. We have also looked into the potential for bias on the parts of the participants.

## 2. GENERAL COMMENTS & OBSERVATIONS

### BRADFORD HILL CRITERIA

#### Biological Criteria

- (1) Plausibility
- (2) Experimental evidence

#### Epidemiological Criteria

- (3) Strength
- (4) Biological gradient
- (5) Consistency
- (6) Specificity

#### Mixed Criteria

- (7) Temporality
- (8) Coherence
- (9) Analogy

We attempted to apply Bradford Hill criteria to assess the material sent to us from the National Toxicology Program subcommittee on Environmental Tobacco Smoke. Given the disparate types of information provided we achieved mixed results in assessing biological and epidemiological data. Of the nine tests proposed by Hill (see box), we found none that convincingly supports the contention that ETS is a human carcinogen.

### The nature of ETS.

According to Volume II (p 1), environmental tobacco smoke (ETS) is the sum of sidestream (SS) smoke (interval between puffs), mainstream smoke (MS) emitted at the cigarette mouthpiece during inhalation,

compounds diffused through the wrapper, and MS that the smoker exhales. Somehow, one is asked to believe the whole (ETS) is greater than the parts (MS) and (SS). Because biological plausibility is the keystone of the argument for listing ETS as a human carcinogen, it is important to understand the nature of both ETS and MS/SS smoke.

In reality, ETS is a highly dilute and diffuse substance. *ETS and mainstream smoke may share components, but their chemical and physical differences are substantial.* Moreover, despite the appearance of long lists of chemical components and yields included in the NTP documents, the presence of most ETS components can only be postulated because they are beyond material detection. The undermines the entire structure of "association by analogy" argument and renders tenuous the concept of biological plausibility upon which much of the material rests.

### Measuring ETS Exposure

None of the epidemiological studies on ETS has provided reliable estimates of doses of ETS exposure. Only rough estimates have been made, limited by the uncertainties of personal or proxy recall of the intensity, frequency and duration for lifetime exposure. Further confounding the results are recognized problems with misclassification of some smokers as non-smokers, study designs that do not account for diet, occupational exposure, socioeconomic status and other variables. Specificity is called into question here since this criterion requires that confounding factors be considered, as well as exposure and response specificity and consistency.

Air monitoring of ETS has been inconsistent -- dependent on the location of the monitor (height from floor), length of time the monitor accumulates data, etc. Dose estimates based on body fluid concentrations of nicotine or cotinine yield higher values, but depend on environmental and pharmacokinetic assumptions of unlikely validity.<sup>56</sup> The estimates by the National Academy and OSHA are based on straightforward material balance concentrations are more credible. Still these estimates for actual exposure are far too high. A study of 100 nonsmoking individuals in 16

metropolitan areas of the U.S. who collected a sample of air from their breathing zone both in the workplace and at home, showed that *actual* exposures of typical subjects to nicotine in the workplace (were) 80-85% *less* those estimated by OSHA for the most highly exposed workers.<sup>7</sup> Home exposures were from 40-70% *less* than OSHA estimates.

Plasma concentration of volatile organics in active smokers appears to be only slightly higher than in non-smokers, indicating significant sources other than tobacco combustion.<sup>8 9</sup> Dr. Bingham, (Transcript p 236), notes that, "... essentially (biomarkers) were the same number for the unexposed and the ETS exposed (compared) with smokers. I would have thought we would have seen some differences." The fact that biomarker measurements are essentially the same between unexposed and ETS-exposed groups, weakens the argument further -- both biologically (experimental evidence) and analogy (the proposed measurement could be analogous to some other factor).

In fact, with the exception of tobacco-specific nitrosamines (TSNA), these biomarkers are related to chemicals that occur ubiquitously in the environment and in food. As a consequence, the background levels in unexposed nonsmokers are high compared to the observed increases (if any) associated with ETS exposure.<sup>10</sup>

Biomonitoring for genotoxic substances, then, does not reveal significant increases for ETS, since many of these genotoxic substances relate to chemicals commonly occurring in the environment and food.

## **Realistic Exposure Levels**

The momentary exposure to ETS encountered by most people is markedly insignificant. On the basis of extrapolations from sidestream smoke data, the National Academy of Sciences calculated that for nicotine alone the difference in peak inhalation concentration between smokers and ETS exposed non-smokers varies between 75,000 and 7,000,000-fold.<sup>11</sup> More conservatively, other measurements (OSHA) indicate that the risk to a typical non-smoker from respirable suspended particles (RSP), compared to the dose of RSP for an active smoker, estimate ETS exposure ranges from 1/75,000 to 1/500,000 that of an active smoker.<sup>12 13</sup>

Using surrogate sidestream smoke values, realistic ETS exposure has been compared with current federal standards of permissible occupational exposure to several smoke components. Considering an unventilated room of 100m<sup>3</sup> (3533 cubic feet), the number of cigarettes that would have to be burned before reaching the official threshold limit values varies among 1,170 for methylchloride to 13,300 for benzene, to 222,000 for benzo(a)pyrene, to 1,000,000 for toluene.<sup>14</sup>

Consider, please, the possibility of finding oneself in a 20' x 22' room with 8' ceiling height along with 1,170 smokers. It begs the imagination. So, too, does much of the material used to 'prove' that ETS is a carcinogen.

Coherence comes into play here -- the proposed relationship does not seem to meet standard threshold requirements. Exposure levels appear to be implausibly low.

## Minimum Threshold

In addition to implying that ETS is somehow more concentrated than mainstream smoke (a patent absurdity that turns on its head the principle of dose-response), there seems to be some underlying assumption that there is no minimum threshold for exposure. We find this surpassing strange. In fact, people who smoke less than 4-5 cigarettes daily may not attain health risks significantly different from those of non-smokers.<sup>15 16</sup> No-effect observations at comparatively high doses are also routinely reported in experimental animal exposures to whole smoke or its fractions.<sup>17</sup> Nyberg *et al.* (1997) states "...light smokers have only a very moderately elevated risk of lung cancer."<sup>18</sup> Again, the material fails biological gradient criteria. In addition, this criteria is not met for dose-response trend, since many studies report a nonmonotonic association (no trend).

## Epidemiological Assessment

A significant majority of the research regarding ETS and human carcinogenicity report NO significant association. At best, such an association has only been suggested by those reporting a positive correlation. Such suggestions have uniformly been reported as extremely weak associations. The U.S. National Cancer Institute has clearly stated that increases of less than 100 percent (RR 2.0) are too small to be relied upon. The consistency criteria is simply not met. There is no question of this. The evidence is patent.

"In epidemiologic research, ...increases in risk of less than 100 percent, [or 2.0] are considered small and are usually difficult to interpret. Such increases may be due to chance, statistical bias, or the effects of confounding factors that are sometimes not evident."

Source: National Cancer Institute, Press Release, October 26, 2994.

## Trend Analysis for Dose Response: Misrepresentation

We were particularly troubled by the misrepresentation of trends for dose-response. For example, in Vol II, p 27, re Fonham, we read that there was a positive trend in risk with increasing packyears. In fact, the trend was nonmonotonic in several categories, for example: Women who were exposed for 1-15, 16-30, and >30 years had adjusted ORs of 1.45, 1.59 and 1.54, respectively (p for trend=0.002)(Table 6 of Fonham *et al.*, 1994.) In another contorted analysis, this same study reports an adjusted OR of 1.86 (95% CI=1.24-2.78) for 31 or more years of workplace exposure, then turns around and lists a an adjusted OR of 1.74 (95% CI= 1.14-2.65) for women with 48 or more years of exposure.

Mention was made in the transcript of the 1997 Hackshaw *et al.*<sup>19</sup> meta-analysis (actually a re-meta-analysis of an existing meta-analysis) of 37 published epidemiological studies of the risk of lung cancer. Careful reading of the report shows that "Data on the dose response relation between the number of cigarettes smoked by the husband and the risk of lung cancer was reported in 16 studies." *That means that less than half of the studies reported a dose response trend.*

Only 11 of the studies found a positive trend for duration of exposure. While the authors attempted to make it appear that only these studies had included exposure and dose data, this was not the case. In fact, a significant majority of the studies reported no trend for dose-response or dose-exposure. Once again, in an effort to 'prove' the point, the criteria for biological gradient has been failed. We are extremely disturbed at the misrepresentation of results.

### **Confounding & Publication Bias**

Confounding factors that include a wide variety of lifestyle risks have been routinely ignored and/or inadequately accounted for in epidemiological studies. Meta-analysis is NOT an appropriate tool to attempt to account for confounders. They must be addressed in the original study design. Even when addressed in the original study however, nearly all of this information on confounding factors was supplied in the form of self-reported, unverified data. We can only ask the reader to honestly ask how accurate the average person's assessment is for dietary fat, Vitamin E or alcohol (often markedly under reported).

There has been a significant bias shown in reporting the effects of ETS and a systematic exclusion of papers and research reports that would tend to refute the contention that ETS presents any significant health problems at all. This bias is expressed in several ways: 1) the tendency to publish 'significant' and 'positive' results, which leads to 2) decisions to not submit work that shows negative or insignificant results, and worse yet 3) the 'cherry picking' of studies to support the hypothesis that ETS is a human carcinogen.

Again, the criteria for specificity demands that confounding factors be addressed. Correctly and adequately addressing these factors could quickly render null or negative any correlations for ETS and lung cancer.

### **Statistical 'Malpractice'**

More troublesome, are the highly questionable statistical standards have been applied to meta-analyses of many highly disparate studies of ETS and lung cancer. This is strikingly apparent in the USEPA and CEPA reports used as background for NTP's decision to rank ETS as a carcinogen. From the USEPA's troubling decision to use a 90% confidence interval to testimony in the NTP transcript lauding such tortuous studies as Well's (1998) which established an arbitrary set of 'quality restrictions' to exclude negative research results, we found egregious examples of statistical misrepresentation, unverified data and uncontrolled confounding risk factors. Conclusions were drawn based upon inadequate and sometimes overstated risk estimates.

### **Inconsistency in assessing significance**

Consistency and strength are missing throughout all of the background material and there are ample examples of incoherence and questionable analogy. For example, we are asked from the beginning to believe that all of the average relative risks over 1.0 are statistically significant (a patent absurdity), yet throughout the background material we find statements that these are not

significant. In Vol II, p 7-29, we read that Shimuze et al., 1988 was significant with an RR of 1.08 (CI 0.64-1.82), while Sobue, 1990 was not with an RR of 1.13 (CI 0.78-1.63).

We are asked to believe that extreme condensates of ETS are equal to an equivalent weight of mainstream smoke (Vol II, p v) and that three studies are significant (Stockwell, 1992; Brownson, 1992; Fonham, 1994), while one that gives similar risk estimates is not (Kabat, 1995)(Vol II, p vi). Yet Brownson reports an overall OR of 1.0 (Vol I, p 7-25), Stockwell's OR includes 1 and is not adjusted for a wide variety of confounding factors. Only Fonham accounted for a majority of confounding factors (OR=1.29, 95% CI=1.04-1.60 ever exposed). However, Fonham measures joint exposure to childhood and adult ETS exposure and *did not acknowledge* the presence of a statistical interaction of these groups that supports the absence of an association between ETS and lung cancer. The Fonham authors acknowledge that these *exposures* may be concurrent, yet made no statistical adjustment for concurrent exposures. Please see "Statistical Malpractice" above.

## Science v Advocacy

Serious scientists concede their hypotheses wrong when confronted with data. Advocates never concede, having started with their conclusions and worked backwards. We believe that the effort to 'prove' ETS a human carcinogen is largely an activist/advocate effort. As a result, an immeasurable amount of damage is being done to the credibility of the scientific community by avowed anti-smoking advocates determined to somehow prove that ETS is a human carcinogen in the face of irrefutable evidence to the contrary.

Smoking is a serious cancer risk. It is implicated in the vast majority of lung cancer cases. The so-called risks of ETS for cancer are immeasurable small. Dancing on the tiny pinhead of statistical insignificance trying to convince us that relative risks less than 2.0 are meaningful is a waste of time and resources. Of the 30 studies addressed by EPA in 1992, only 23.3% show statistically valid positive correlations for ETS and lung cancer. Of these, only five had adjusted RRs of 2.0 or greater. The test for strength fails utterly. "If the relative risk is 'strong', there is less likelihood that there are other adequate explanations of the observed association. In checking this criterion we will also need to consider influence of chance, study quality, confounders and the possibility of publication bias."<sup>20</sup>

## Scientific Misconduct

In our effort to understand how ETS came to be labeled a carcinogen in the absence of consistency, sound analogy, coherency and exposure-response trends, experimental evidence and strength, we researched the history of the process to declare ETS a carcinogen within the context of public health policy.

The movement to eradicate smoking has proceeded in three distinct phases, according to Richard Daynard, a well-known and highly paid anti-smoking activist.<sup>21</sup> First, following the 1964 Surgeon General's Report, activists attempted to persuade smokers to stop smoking on the basis that

smoking was bad for the smoker. This was largely an education process and was quite successful in reducing the incidence of smoking in the U.S. Cigarette smoking declined more among men than among women between 1965 and 1990. The age adjusted smoking prevalence declined at an average annual rate of 2.4% for men and 1.5% for women.

Second, activists attempted to make smokers feel guilty about their enjoyment of smoking. This phase was far less successful in reducing the incidence of smoking. Rates declined less than during this period for both men (29%) and women (24%).

Third, the movement began to focus on the "development of evidence" about ETS (see comments under "Witchfinding"). If people can be "convinced" that tobacco smoke is harmful to nonsmokers, it becomes easier to "persuade" individual, businesses and government authorities to restrict or ban smoking, thus "undercut(ing) the social support network for smoking by implicitly defining smoking as an antisocial act."<sup>22</sup> This has been markedly unsuccessful inasmuch as smoking rates have not fallen (28% men, 23-25% women)<sup>23</sup> while youth smoking has markedly *increased* since the inception of the ETS "message" following the EPA's 1992 report on environmental tobacco smoke.

We believe that advocacy should always bow to science. To do otherwise is to undermine the credibility of all scientists and to promulgate unnecessary and unwieldy public health policy. By identifying the stages of anti-smoking advocacy and comparing it to the rates of smoking in the U.S., it becomes apparent that even the general population knows the difference between advocacy and science and chooses to ignore the former when the later is corrupted.

## **Law of Unintended Consequences**

The tangled web of misrepresentation about the nature of ETS and its health risks has, we think, resulted in several unintended circumstances. First and foremost, of course, is the increased rate of smoking initiation among teens and young adults in the U.S. Hundreds of millions of dollars have been thrown at the teen smoking 'problem,' resulting in a marked skepticism within these population groups. It is reminiscent of the overall public amusement over the scientifically ridiculous film "Reefer Madness."

The incidence of first daily cigarette use among persons aged 12-17, which had fluctuated slightly from 1966 (42.6%) to 1983 (43.8%), began to increase from 1988 (51.2) to 1996 (77.0)<sup>24</sup> -- stages two and three of the anti-smoking activists' agenda. There appears to be an inverse correlation between the amount of anti-smoking advocacy and questionable science and the incidence of youth smoking. Perhaps our children are better educated in science and mathematics than we have been led to believe. They certainly are attracted to the idea of "forbidden fruit." It might be well to allow the possibility that we have reached an irreducible minimum in smoking levels with sound educational programs and that scare tactics and contorted scientific theories result in skepticism and disdain.

A second possible consequence came to light quite by accident as we researched the history of the ETS conundrum and looked at rate-of-smoking statistics and other health risk factors. It appears

that the prevalence of overweight<sup>25</sup> in the U.S. is inversely proportional to the rate of smoking, crossing over at 1975. Have we traded one health risk for another? In terms of the rather grotesque tendency to reduce citizens to units of health care costs, it may be far more costly to address the chronic and debilitating effects of obesity.

The third consequence, and by far the most serious in our opinion, is the utter disdain with which much scientific research is now received by the general public. The phrase "junk science" has become commonplace. We see references to "the government's daily health scare" in editorials and cartoons. The EPA itself is under intense scrutiny for what can only be called scientific malpractice -- setting policy before the research is completed in a variety of instances. The nonpartisan U.S. General Accounting Office and Congressional Research Service (CRS) have been highly critical of the USEPA -- on the issue of ETS as well as other matters. In reviewing the CRS comments on USEPA/ETS (1992) in their report "Environmental Tobacco Smoke and Lung Cancer Risk (Nov 14, 1995), we found confirmation of several of our major concerns regarding the material.

"... it is possible that very few or even no deaths can be attributed to ETS" (p 55 -- CRS), ...the dose response trends reviewed by the EPA are "not definitive" and even at the highest exposure levels, the reported risks are "subject to uncertainty"(p 2)...smoker misclassification could explain all the measured risk even at high exposure levels..." (pp 40-41)... "it is clear that misclassification and recall bias plague ETS epidemiology studies" (p 45)... 'Many studies did not control for any aspect of socioeconomic status, and most that did use such controls did not use the most general one income. Absence of controls for this factor would tend to exaggerate the relationships...' (p 70).

In short, politicized science is not science at all. And the listing of ETS as a carcinogen is clearly politicized science.

### 3. QUALITY OF MATERIALS

Each of these documents (Volumes I, II and Transcript) have serious flaws. What is more, flaws from earlier reports are exacerbated in later reports. There is an almost geometric progression of faulty logic. It is rather like a game of "Whisper" wherein the original statement is misinterpreted, re-misinterpreted, *ad infinitum*. The final conclusion bears little relationship to the original material. Overall we found a disturbing pattern of ignoring the full available body of scientific literature. In addition, there were serious misrepresentations of prior conclusions and a systematic effort to discount material from industry as somehow 'tainted' while ignoring several egregious misstatements and clear bias on the part of publicly avowed 'anti-smoking' advocates.

Even limited ourselves to the one-sided material included in the background material, *we find no convincing evidence that ETS is a human carcinogen*, as summarized in our discussion of Volumes I and II, as well as our review of the transcript of the subcommittee. When we extended our research in an attempt to reconstruct the process by which ETS has been implicated as a carcinogen, it became sadly clear that the risk assessment process has been corrupted by a



predisposition toward 'proving' a positive association between ETS and human carcinogenicity, when no such association is scientifically supported.

## Volume I

1. The IARC (1986) report (which was largely a compendium of material on mainstream smoke rather than environmental tobacco smoke exposure) found that the available evidence was *insufficient to draw a conclusion* regarding ETS and cancer. This accurate observation was restated unequivocally in Section 3.5 (Discussion) of NTP's own draft document (Vol II, pp 43).

IARC's conclusions are clearly negative for any association between ETS and lung cancer, since the positive studies showed no dose-response relationship, thus throwing their results into the "no association" category. IARC concludes (Vol I, p 314) that "The amounts (of ETS) absorbed by passive smokers are, however, small, and effects are unlikely to be detectable..."

The absence of any consistent dose-response relationships puts into question the biological plausibility of the hypothesis that ETS causes lung cancer. The large number of negative correlations (bounds including 1) for ETS and lung cancer raises the possibility that ETS is a protective factor for lung cancer -- especially for childhood exposure.

However, on the whole, none of the results were statistically significant, inasmuch as few showed any relative risks or odds of risk over 100% (or 2.0), which, according to accepted standards, is the very least one could expect to see (and that on a consistent basis) before considering statistical significance.

"The strength of association relates to causality. Relative risks of less than 2.0 may readily reflect some unperceived bias or confounding factor, those over 5.0 are unlikely to do so."

Breslow, Day *Statistical methods in cancer research. Vol 1: The analysis of case control studies.* IARC Sci Pub No 32, Lyon 1980. (P 36)

The IARC report appears to have been included to add heft to the physical document. There is no question that cigarette smoking is implicated in lung cancer and *perhaps* in other human cancers. The question under discussion, however, is ETS not primary smoking.

2. The USEPA's 1992 report has so many methodological flaws and contains so much misrepresentation that we hardly know where to begin our comments.

3. The CEPA's 1997 report is built largely upon the questionable results of the EPA's 1992 report. In addition, the CEPA report includes animal study results using concentrations of tobacco smoke that far exceed any exposure that humans could reasonably be expected to experience. Even then, according to Vol. II (p 47), "Exposure to tobacco smoke had no effect on pulmonary tumor incidence or tumor multiplicity."

"(e)pidemiological observations... have serious disadvantages... (T)hey can seldom be made according to the strict requirements of experimental science and therefore may be open to a variety of interpretations. A particular factor may be associated with some disease merely because of its association with some other factor that causes the disease, or the association maybe an artifact due to some systematic bias in the information collection... It is commonly, but mistakenly, supposed the multiple regression, logistic regression, or various forms of standardization can routinely be used to answer the question: 'Is the correlation of exposure (E) with disease (D) due to merely a common correlation of both with the same confounding factor (or factors) ?... Moreover, it is obvious that multiple regression cannot correct for important variables that have not been recorded at all... The disadvantages limit the value of observations in humans, but... until we know exactly how cancer is caused and how some factors are able to modify the effects of others, the need to observe imaginatively what actually happens in various different categories of people will remain..."

(Doll R, Peto R. The causes of cancer, JNCI 66:1192-1321, 1981. P. 1281)

Because so much of the material in these two documents is simply repetitive, and because so much of the material is not relevant (dealing largely with mainstream smoke), we have combined our comments for these two reports. Each of them has significant flaws from both epidemiologic and statistical standpoints. In the absence of raw data from the studies involved, we have obtained copies of the studies themselves, or abstracts where the studies were not available on such short notice.

It is certainly not our intent to disparage epidemiologists. We do, however, suggest that the association

between ETS and lung cancer (or any other cancers for that matter) lie largely in realm of what Doll and Peto call "the need to observe imaginatively."

Our deepest concern is for the apparent disregard of basic tenets of sound science and an apparently willful manipulation and misrepresentation of statistical data to meet preordained "conclusions."

We have organized our comments generally around the transcript, addressing Volumes I and II as we do so.

On the basis of review, not only of the background material supplied, but also of the primary material used to develop the background (as well as material EXCLUDED from the background), we conclude that any risk from ETS is immeasurably small.

**Only 16.6% of the 30 studies show any significant association.**

AUTHOR	YEAR	LOCATION	NO. OF LUNG CANCERS	SEX OF SUBJECT	AVG RR	RR (95% CI)
Akiba	1986	Japan	94 19	F M	1.50 1.80	(0.90-2.80) (0.40-7.00)
Brownson 1	1987	USA	19	F	1.68	(0.39-6.90)
Buffler	1984	USA	41 11	F M	0.80 0.51	(0.34-1.90) (0.14-1.79)
Chan	1982	Hong Kong	84	F	0.75	(0.43-1.30)
Correa	1983	USA	22 8	F M	2.07 1.97	(0.81-5.25) (0.38-10.32)
Fontham*	1994	USA	651	F	1.29	(1.04-1.60)
Geo	1987	China	246	F	1.19	(0.82-1.73)
Garfinkel 2	1985	USA	134	F	1.23	(0.81-1.87)
Gong	1988	China	54	F	2.16	(1.08-4.29)
Humble	1987	USA	20 8	F M	2.20 4.82	(0.80-6.60) (0.63-36.56)
Inoue	1988	Japan	22	F	2.25	(0.80-8.80)
Janerik	1990	USA	144 44	F M	0.75 0.75	(0.47-1.20) (0.31-1.78)
Kabat 1	1984	USA	24 12	F M	0.79 1.00	(0.25-2.45) (0.20-5.07)
Kalandidi	1990	Greece	90	F	2.11	(1.09-4.08)
Koo	1987	Hong Kong	86	F	1.64	(0.87-3.09)
Lam T	1987	Hong Kong	199	F	1.65	(1.16-2.35)
Lam W	1985	Hong Kong	60	F	2.01	(1.09-3.73)
Lee	1986	UK	32 15	F M	1.00 1.30	(0.37-2.71) (0.38-4.39)
Liu Z	1991	China	54	F	0.77	(0.30-1.96)
Pershagen	1987	Sweden	70	F	1.20	(0.70-2.10)
Shimizu	1988	Japan	90	F	1.08	(0.64-1.82)
Sobue	1990	Japan	144	F	1.13	(0.78-1.63)
Svensson	1989	Sweden	34	F	1.26	(0.57-2.81)
Trichopoulos	1983	Greece	77	F	2.08	(1.20-3.59)
Wu	1985	USA	29	F	1.20	(0.50-3.30)
Wu-Williams	1990	China	417	F	0.70	(0.60-0.90)
Butler (Coh)	1988	USA	8	F	2.02	(0.48-8.56)
Garfinkel 1 (Coh)	1981	USA	153	F	1.17	(0.85-1.61)
Hiramaya (Coh)	1984	Japan	200 64	F M	1.45 2.24	(1.02-2.08) (1.19-4.22)
Hole (Coh)	1989	Scotland	6 3	F M	1.89 3.52	(0.22-16.12) (0.32-38.65)

\*We used the 1994 Fontham data, rather than the preliminary 1991 report. Only 23.3% of these studies show any statistically valid positive correlation for ETS and lung cancer. Of the 30 studies, only seven had lower bounds of 1.0 or greater. Of these seven, only five show an adjusted RR of over 2.0. Thus only 16.6% of the studies actually support the contention that ETS is a carcinogen.

**Figure 2**

In main, we found that of the 30 studies involved, only seven or 23.3% show any statistically valid positive correlation for ETS and lung cancer, with lower bounds of 1.0 or greater. Of these seven only five (actually four and one-half, since Hiramaya is significant only for a small group of men) showed an adjusted relative risk of over 2.0. Thus only 16.6% of the studies actually support the contention that ETS is a carcinogen. With the exception of Fontham, their small size should have rendered their weight in the analysis as quite small. This is hardly compelling evidence upon which to base a listing for carcinogenicity. See Figure 1.

Because the Fontham study did appear to show a positive (although weak) association for ETS and lung cancer, we searched for raw data or informed comments on this study. We were unable to get raw data but were able to locate substantive comments for both Fontham and a later Brownson study. These comments, as well as our observations are included later in this paper. The reanalysis is not favorable for listing ETS as a carcinogen, however, since the results are an Odds Ratio 1.0 (or no significance) for the two categories of women with adult exposure. See Figure 2.

The Fontham study examined the joint exposure to childhood and adult ETS exposure. We believe CEPA was remiss in not addressing the manner in which Fontham *et al.* conducted and presented those analyses because Fontham *et al.*, while acknowledging the exposures could be concurrent, *did not acknowledge* the presence of a statistical interaction that supports the absence of an association between ETS and lung cancer. See Figure 2.

Data from Fontham *et al.*, (1994, Table 8),

Crude Association of Lung Cancer with ETS Exposure, Restricted to Self-Respondents

(a) Case Control								
Adult ETS Exposure			Childhood ETS Exposure					
			No			Yes		
No			23/71			5/44		
Yes			118/364			235/724		
(b) ORs & 95% CI								
Adult ETS Exposure			Childhood ETS Exposure					
			No			Yes		
No			1.00 Baseline			0.35 (0.12, 0.99)		
Yes			1.00 (0.60, 1.67)			1.00 (0.61, 1.64)		

Figure 2

The Fontham study examined the joint exposure to childhood and adult ETS exposure. The CEPA report cites the results of Fontham's analysis of that joint exposure as presented in Table 8 of the article of Fontham et al. CEPA was remiss in not addressing the manner in which Fontham et al. conducted and presented those analyses because Fontham et al. *did not acknowledge* the presence of a statistical interaction that supports the absence of an association between ETS and lung cancer.

"If the confidence interval includes 1, then the difference in the effect of experimental and control treatment (or effect) is **not significant at conventional levels**  $P > 0.05$ )"

Egger et al, Meta-analysis principles and procedures, *BMJ* 1997; 315(7121):1533

This material is equally pertinent to the USEPA findings for ETS.

## Volume II

Volume II is a curious document. It is loaded with detailed charts and tables about the physical and chemical properties of ETS and mainstream smoke as well as information about biomarkers. Volume II is marred by three major failings:

1. Invalid assumptions about the nature of ETS
2. Misrepresentation of statistical significance.
3. Exaggerated conclusions regarding limited animal studies
4. Inclusion of material that appears designed to alarm, but is, in fact, largely benign.

Both Volumes I and II contained an extraordinary amount of detailed material about the chemical components of mainstream and sidestream (ETS) smoke. None of this was particularly informative. With surpassing few exceptions most of these compounds are readily identifiable in wood smoke, kitchen air exhaust, automobile exhaust and other forms of combustion.

## Biomarkers

On page 9 of this volume it is noted that "*Some of these biomarkers have limited usefulness because they have short half-lives in the body.*" These measurements can provide inflated exposure estimates when environmental influences such as diet, diesel pollution, chemical plant waste, and natural burning (campfires, wood, etc.) contribute to biomarker concentrations." We agree.

Much is made cotinine, a metabolite of nicotine specific to nicotine, tomatoes, potatoes, eggplant and certain teas. We are puzzled by the statement on page 9 that "(a)ssessments of serum samples collected as part of the NHANES III survey revealed that 91.7% of the US population over 4 years of age had detectable serum cotinine levels indicating exposure to tobacco smoke through active or passive smoking (Pirkle et al. 1996)." *Since only 25-28% of the U.S. adult*

*population (98% of smokers) smokes. few workplaces permit smoking in the general work area, most restaurants have separate smoking accommodations and one hardly expects tobacco exposure in day care centers or schools, how exactly are children over 4 be regularly exposed to tobacco smoke?* These types of unscientific blanket, summary indictments of ETS as some sort of wildly toxic, omnipresent miasma alerted us to a strong possibility of political or emotional bias on the part of those compiling information about ETS.

Again, on page 9, we note that “(c)otinine levels in body fluids are more typically measured than are those of nicotine because cotinine has a longer half-life (16-20 hour vs. 1 hour) in the body (Scherer and Richter 1997).” If biomarkers are so important (which we do not believe they are except as an expensive surveillance tool), then *the absence of a biomarker past a few hours indicates to us that the human body is quite capable of handling any minute burden placed upon it by ETS.*

It is interesting, with all the emphasis on biomarkers in this volume, that the initial summary statement is quite clear that *“there is no good biomarker of cumulative past exposure to tobacco smoke, and all of the information collected in epidemiology studies determining past exposure to ETS relies on estimates which may vary in their accuracy (recall bias).”* (Page v) Again, if there is no biomarker of past exposure, this indicates that the human body is well prepared to handle the tiny burden placed upon it by ETS.

### **Confounders are routinely ignored.**

On page 43 of Volume II, it states *“a number of systematic biases have been proposed to account for this small increase in risk (of ETS for cancer).”* The document goes on to state that issues of confounding have been taken into consideration in several studies. They have not. The number of confounding factors that could influence this type of very small risk are routinely ignored. In only one study (Fontham, 1994) were selection bias, misclassification of former or current smokers as non-smokers, misclassification of non-lung cancer as lung cancer, dietary or vitamin factors, age, race, study area, education, family history or employment in high-risk occupation considered. Fontham (1994) reports an adjusted RR of 1.29. Reanalysis of this adjusted RR, for all combinations of exposure achieves a markedly different conclusion of 1.0 (precisely no effect). We discuss wandering and inappropriate baselines later in this paper under the topic heading of “7<sup>th</sup> Day Adventists.”

### **Dietary confounders are inadequately considered**

In the Fontham (1994) study, much is made of ruling out confounders, yet in the matter of dietary confounders, the researchers inadequately considered dietary fat, vegetable/fruit intake and vitamin supplementation. Indeed, the risk for dietary fat and lung cancer appears to be significantly greater than that of ETS.

Far more important is the fact that high fat diets have been demonstrated to increase the incidence

of lung cancer. "Dietary intake of saturated fat was the leading identified cause of lung cancer among lifetime nonsmokers and former smokers in Missouri,"<sup>26</sup>

Adenocarcinoma of the lung has been associated strongly with saturated fat intake (odds ratio [OR] = 2.3, 95 percent confidence interval [CI] = 1.2-4.4), whereas small-cell lung cancer has been associated with dietary cholesterol (OR = 2.8, CI = 1.1-7.5).<sup>27</sup>

Certainly this matter deserves much more careful consideration before ETS is listed as any kind of carcinogen, much less Class A.

### **The beta-carotene controversy**

At the time of the Fontham study, beta-carotene was thought to be protective for lung cancer. Later research indicates that beta-carotene (at least in supplemental or vitamin form) can actually increase the incidence for lung cancer. In the absence of raw data and calculations, we can only ask the question: Did Fontham factor positively for beta-carotene, when in fact, it should have been factor as a negative or null confounder? When you are dealing with such markedly weak associations (Fontham, RR 1.19), then tiny differences have a large impact in the final calculations. We begin to suspect a predisposition to find ETS a risk factor when, in fact, it is not. All of the diseases addressed -- from cancers to respiratory and cardiovascular diseases -- are complex and multifactorial. Again and again, we find the process of 'finding' ETS carcinogenic extremely biased and unscientific.

### **Heredity**

While family histories were taken in several studies, the role of predisposition for all types of cancer is uncertain. It has been suggested that the contribution of heredity to the cancer burden is greater than generally accepted, and that study of heritable predisposition will continue to reveal carcinogenic mechanisms important to the development of all cancers.<sup>28</sup>

### **Socioeconomic status**

Socioeconomic status plays a far greater role in mortality than is recognized in the body of work surrounding ETS and lung cancer. "Although reducing the prevalence of health risk behaviors in low-income populations is an important public health goal, socioeconomic differences in mortality are due to a wider array of factors and, therefore, would persist even with improved health behaviors among the disadvantages,"<sup>29</sup> according to a nationally representative prospective study of US adults. This study (Lantz *et al* 1998), reports hazard risk ratios ranging from 3.22 (95% CI,=2.01-5.16 for those in the lowest income group and 2.34 (95% CI=1.49-3.67) for those in the middle income group -- after controlling for age, sex, race, urbanicity, and education. Please note: these are truly statistically significant results. One is not included, and the RRs are over 2.0.

## Physical Activity

Physical activity has *never* been adequately factored into the ETS equation. Yet a large study of more than 81,000 men and women showed a protective factor of physical activity for lung cancer.<sup>30</sup> In this sub-cohort, physical activity was assessed twice at an interval of 3 to 5 years. Leisure but not work activity was inversely related to lung-cancer risk in men after adjustment for age, smoking habits, body-mass index and geographical residence ( $p$  for trend = 0.01). Men who exercised at least 4 hours a week had a lower risk than men who did not exercise [relative risk (RR) = 0.71; 95% confidence interval (CI) = 0.52-0.97]. Reduced risk of lung cancer was particularly marked for small-cell carcinoma (RR = 0.59; 95% CI = 0.38-0.94) and for adenocarcinoma (RR = 0.65; 95% CI = 0.41-1.05). Interestingly, these reduced risk figures are similar to the reduced risk figures for lung cancer reported for children exposed to ETS.

Far more study should be undertaken on the protective benefits of physical activity overall, but certainly in the case of ETS. We have stated several times that ETS exposure is only one of a common cluster of risk factors, especially in spousal studies.

## Alcohol

The association between alcohol consumption and lung cancer has received slightly more attention in several studies. We do not think that it has been adequately factored out, however. Drinkers of more than 12 beers per month have been shown to be 1.6 times more likely to develop lung cancer than nondrinkers of beer after controlling for age, years of education, and cigarette smoking (95 percent confidence interval = 1.0-2.4,  $P$  for trend = 0.003).<sup>31</sup>

We found it refreshing to read in one study that implicated alcohol consumption in lung cancer that "Although we devoted considerable efforts to adjusting for smoking in our analyses, residual confounding is still possible *because smoking and alcohol are closely associated*. In addition, case-control studies including this study should be viewed with caution because of possible selection bias."<sup>32</sup> Despite the fact that there appears to be a multiplicative effect for alcohol and smoking, these careful researchers acknowledged the potential for bias and residual confounding. We strongly suggest that NTP do the same.

"Drinkers of more than 12 beers per month have been shown to be 1.6 times more likely to develop lung cancer than nondrinkers of beer."

Bandera *et al.* Alcohol consumption and lung cancer in white males. *Cancer Causes Control* 1992 Jul 3:4 361-9.

Few studies in Volume II show any statistical significance despite the fact that the summary concentrated on a few selected studies. There is a tremendous difficulty in making any sense between the studies listed between the volumes. No consistent format has been used. No consistent expression of results has been established. Some RRs are corrected, some are not.



*Of the 43 various cancer site studies summarized in Volume II (pp 32-42), only nine acknowledged potential confounding effects.* One of the largest lung cancer studies (Cardenas et al, 1997, 77,000 M/F never smokers, CPS-II), was adjusted for a number of confounders, but was limited to a large group of self-selected respondents who were not typical of the general population. Even then, the results were non-significant (95% CI, 0.8-1.6, RR = 1.2). The trend analysis was negative for dose-response.

Studies attempting to associate ETS with any other cancer than lung cancer were simply too small, combined active and passive smokers, showed no dose-response by smoking rate or duration. On bladder cancer, CI information on Burch was not available.

Again, there was no convincing evidence of the carcinogenicity of ETS for any type of cancer.

### **Animal Studies**

The National Research Council and the USEPA have both recommended improvements in the risk assessment process that involve incorporating consideration of dose to the target tissue, mechanism of action, and biologically based dose-response models, including a possible threshold of dose below which effects will not occur.<sup>33</sup> We find that there is no evidence of a consistent dose-response trend for ETS and any human cancer site. Nor are animal tests cited in the background material convincing for ETS carcinogenicity.

*"Testing for carcinogenicity at near-toxic doses in rodents does not provide enough information to predict the excess number of human cancers that might occur at low-dose exposures.* Testing at the maximum tolerated dose (MTD) frequently can cause chronic cell killing and consequent cell replacement (a risk factor for cancer that can be limited to high doses), and ignoring this effect in risk assessment greatly exaggerates the risks."<sup>34</sup>

"...rodent bioassays provide little information about mechanisms of carcinogenesis and low-dose risk."

Gold LS et al (28)

Animal studies cited (Witschi et al, various) used injectable concentrates of carcinogens, intense concentrations of tobacco smoke and skin application of tobacco smoke condensate. Not only do these studies bear no relation to inhalation of ETS, they also use concentrations that are so high that nearly any substance in these concentrations could be expected to cause deleterious effects.

We feel it important to note here that *the authors of the A/J mouse studies state, "the usefulness of our animal model for the study of human tobacco smoke induced lung cancer remains to be established."* We agree.

### **SOUND SCIENCE:**

"As a general rule of thumb, we are looking for a relative risk of 3 or more (before accepting a paper for publication)."

Marcia Angell, Editor, New England Journal of Medicine.

"... my basic rule is that if the relative risk isn't at least 3 or 4, forget it."  
Robert Temple, Director of Drug Evaluation, US FDA.

In addition, Volume II includes animal study results (heavily relied upon according to the transcript) using concentrations of tobacco smoke that far exceed any exposure that humans could reasonably be expected to experience. Even then, despite the intense concentrations of condensates "*Exposure to tobacco smoke had no effect on pulmonary tumor incidence or tumor multiplicity.*" Vol. II (p 47).

We were not particularly surprised at the Witschi protocol that showed an increase in tumor incidence when A/J mice were allowed to recover for four months after exposure. This is consistent with the long lead time associated with *primary smoking*. The concentrations used were in excess of those experienced by active smokers. ETS is extremely diffuse and dilute compared to mainstream smoke.

We did mark Witschi's observation that "animals exposed to cigarette smoke lost approximately 17% of their beginning body weight... gained weight at a similar rate as controls... however, never fully regained their body weight." (Vol II, p 48). We, too, think it a good idea to limit adult activities such as smoking to those age 18 or older -- at a time when human growth is largely completed. There is certainly no indication that exposure to real-life ETS concentrations would limit human growth.

All substances are toxic in quantity. Many therapeutic medications are acutely toxic, but beneficial when used at a therapeutic level. Water, oxygen, and table salt are toxic in large enough doses. The mere presence of a substance does not imply toxicity. We do not feel that the material under discussion supports a listing of ETS as a carcinogen.

- ☐ Animal studies were limited to one model. The authors state: "*Exposure to tobacco smoke had no effect on pulmonary tumor incidence or tumor multiplicity.*"
- ☐ There is no consistent pattern of dose-response trend.
- ☐ The relative risks reported are simply so small that they can easily be discounted for factors such as confounding, recall or selection bias, misclassification, or publication bias.

## Transcript

The transcript of the ETS portion of the NTP Board of Scientific Counselors Report on Carcinogens Subcommittee was an eye-opening document. Its contents led us to investigate the history of the topic of ETS as a carcinogen more thoroughly than we might otherwise have done.

A disturbing tendency to underrate some studies and overrate others was evident on the part of the subcommittee members. There were veiled *ad hominem* references to sources of funding

which appeared to imply bias on the part of presenters who questioned the validity of listing ETS as a carcinogen. Why, we wondered was no such bias suggested for the participants who promoted the listing of ETS as a human carcinogen? This led to our investigation of affiliations of the subcommittee members themselves. We concluded that institutional and government affiliations were more highly predictive of biased conduct than was industry affiliation.

We had originally intended to comment only upon the scientific merits (or lack thereof) for listing ETS as a human carcinogen. Our review of the transcript and our subsequent research resulted in a rather more philosophical overview as well. In addition, we found a surprising lack of understanding of basic tenets of epidemiology and meta-analysis on the parts of several subcommittee members as evidenced in their recorded statement.

#### **4. POINT-BY-POINT DISCUSSION**

##### **BIOLOGICAL CRITERIA: Plausibility & Experimental Evidence**

There was a limited amount of time available to make public comments and we would like to make it clear here that we are not singling out Drs. Bucher, Zahm and Yamaski. Their presentations simply appeared first in the transcript and are, in fact, representative of the presentations made by most of the subcommittee members. Indeed, we thank Dr. Zahm for suggesting Bradford Hill criteria of judging causality of epidemiologic data. (Transcript p 181)

**Analysis by analogy** Dr. Bucher begins by making the association by analogy that ETS is a combination of sidestream smoke (SS) and mainstream smoke (MS) not inhaled by the smoker. Yet ETS only contains higher amounts of some of the components of cigarette smoke in general *only when it is obtained in its undiluted form under laboratory conditions* (CDC/DHSS 1989)<sup>35</sup>. This CDC document further states that "ETS is diluted in the air before it is inhaled and thus is less concentrated than MS." Further, "... on the basis of urinary cotinine concentrations, the NRC [1986] concluded that non-smokers exposed to ETS absorb the equivalent of 0.1 to 1.0 cigarettes a day. On the basis of 1985 data, NIOSH estimates that each cigarette smoker in the US smokes an average of about 21 cigarettes a day. Blood and urine samples analyzed for vapor phase nicotine indicate that nonsmokers exposed to ETS absorb about 1% of the tobacco combustion products absorbed by active smokers [NRC 1986: DHHS 1986]." However, if the urine and blood samples are accurate, that would indicate that, at most, ETS would account for only 0.21 cigarette over exposure to 21 cigarettes on average. This is a minute challenge to the body and may help explain the apparent protective effects for ETS exposure in childhood.

In his subcommittee testimony, Dr. Philips reports that average ETS exposure is as little as five to six cigarettes per year. We were unable to get complete copies of his studies in time to assess them for these comments. However, the exposure levels he reports are based on actual monitoring rather than mathematical conjecture and, in our opinion, more likely to be more accurate than our extrapolations above.

**Direct smoking & condensates** The fact that undiluted, concentrated ETS is compared to MS/SS smoke renders the comparison effectively moot. Recall please, that the biomarkers for ETS exposed and non-exposed subjects are nearly identical.

**4,000 chemicals** Of these 4,000 chemicals, only a few are detectable in dilute form. Urine cotinine measurements between ETS exposed and non-exposed women show no difference.<sup>36</sup> It would seem that of these 4,000 dread chemicals (most of which occur ubiquitously in the environment), ETS biomarkers show no evidence of measurable exposure. Benzo(a)pyrene (BaP), which is frequently cited as a dangerous component of ETS, is one of these ubiquitous chemicals. Human beings absorb between 1000 and 5000 nanograms of BaP every day. It is in our water, in our leafy vegetables -- indeed, approximately 2500 ng are released whenever a steak is grilled. According to NTP Vol II (p 2), a typical cigarette yields 0.2 $\mu$ g of BaP.

**Hecht** In the matter of DNA adducts, a study of personal air monitoring of carcinogenic polycyclic aromatic hydrocarbons (PAH) showed *no significant difference in DNA adduct levels between non-smokers and smokers for RSPs (<2.5 microns)* after controlling for exposure to ETS via urine cotinine.<sup>37</sup>

### **FAILED: Biological Criteria -- Plausibility**

**Witschi animal studies** The work cited did not even use ETS or even a reasonable surrogate. Aging and dilution make an enormous difference in the true nature of the substance and have a major impact on the chemical and physical properties of ETS.<sup>38</sup> The 87 mg/m<sup>3</sup> concentration for respirable suspended particulates (RSP) appears to be as much as 3,000 times the concentration likely in any normal indoor exposure situation. "Exposure to ETS were measured by RSP (<2.5 microns) and averaged 242 pg/m<sup>3</sup>," according to NRC 1986. That's picograms -- one-trillionth of a gram. Or 0.000000000242. Why, we wonder, were picograms used? To make the RSP concentration look larger than it was? It has been incredibly difficult to fight our way through the conflicting information and misrepresentations of data.

The authors of the Witschi study concluded that "the usefulness of our animal model for the study of human tobacco-smoke induced lung cancer remains to be established." We agree.

### **FAILED: Biological Criteria -- Experimental Evidence**

## **EPIDEMIOLOGICAL CRITERIA -- Strength, Biological Gradient, Consistency, Specificity**

**90% confidence interval** We were alerted by this testimony to the 90% confidence level used by the EPA. Since so many of the studies involved showed a confidence interval that included 1,

the logical (since it implies a protective effect for ETS) decision would have been to continue to use the two-tailed test with 95% CI used by a majority of the studies. The results would then have been null or negative for association of ETS and lung cancer.

**Fontham** Dr. Bucher notes that the Fontham (1994) study “is considered to be the best study in the literature at this time.” We certainly can agree on that point. Where we diverge is at the very significant point that Fontham *et al.*, overstated the risk estimates by not adjusting for confounding by uncontrolled and unaccounted for nonoccupational exposures to ETS, including exposures in the household and social settings. When this adjustment is made, the association is null, that is 1.0.

**Publication bias** “One of the better publication (on publication bias) is that of Bero *et al.*, 1994 when they did an exhaustive search for unpublished studies on environmental tobacco smoke. . . they concluded that there was no publication bias.” Looking, however, a 1998<sup>39</sup> article, co-authored with Misakian, Bero concludes “There is publication delay for passive smoking studies with nonsignificant (negative or null) results compared with those with significant results. . . 14 of 61 studies were unpublished. . . When studies with human participants were analyzed separately, *only statistically significant (positive) data were predictive of publication.*”

Additionally, “positive-outcome bias was evident when studies were submitted for consideration and was amplified in the selection of abstracts for both presentation and publication, neither of which was strongly related to study design or quality,” according to Callahan *et al.*<sup>40</sup> “Other contributors to *JAMA*’s issue on peer review illustrate the worrying number of biases by which peer review is beset, including nationality bias, language bias, specialty bias and perhaps even gender bias, as well as the recognised bias (citing Bero) toward publication of positive results.”<sup>41</sup>

Since the transcript contained several unpleasant comments suggesting that non-committee presenters were somehow tainted by tobacco-company funds, we would like to point out that Bero receives substantial grants from California’s Tobacco-Related Disease Research program funded with cigarette and tobacco surtaxes [award 2KT0072 for a study of publication bias on environment tobacco smoke which oddly did not find evidence of bias]. Could this not suggest a vested interest in promoting anti-tobacco sentiment in order to gain voter support for increasing excise taxes?

**Smoking in the workplace/Wells** In the transcript (p 177), Dr. Bucher notes that “a number of meta-analyses that have been done to this point had not shown significant increases due to occupational exposure to ETS.” He then goes on to quote a paper by A. Judson Wells, PhD, who stated (based on what we have determined to be highly unstable conclusions) that “USEPA has concluded that smoking is causally associated with lung cancer. . . that means that exposure to environmental tobacco smoke *should* cause lung cancer regardless of locale.” Five recent meta-analyses had recently become available, showing no association between lung cancer and workplace exposure to ETS (combined RRs from 0.98 to 1.04, with an average of 1.01 (95% CI=0.91-1.11).

Wells created six criteria to exclude nine of 14 studies on occupational exposure to ETS, ending up with four extremely small studies, plus a study by Reynolds P *et al* which we simply could not find anywhere. The reference in Wells' paper is to a LETTER that appeared in *JAMA* 1996;275:441-442. Possibly this referred to a 1991 study, "Lung cancer in nonsmoking women: a multi center case-control study," in which Reynolds was a co-author along with Correa, Fontham, Wu-Williams, Greenbert, Buffler and Chen? Since this was the largest of the five studies (528 cases v. 28 for Wu, 90 for Shimizu, 89 for Kalandidi and 99 for Kabat), we can only guess at the quality of the study. Wells' criteria included that no more than 50% surrogate responses for cases be acceptable. Given the high recall bias in epidemiologic studies, that is hardly a reassuring figure when we are dealing with such weak associations. Frankly, it appears that Reynolds was chosen for its size and OR/RR (they are different, but Wells does not acknowledge the fact that an OR always leads to overestimating any RR that is greater than 1, and the degree of exaggeration can be substantial).

The most damning thing we can say about the Wells study is said by the author himself: "... the other four studies had combined workplace relative risks of 1.21 (95% CI=0.91, 1.62) for men and women combined and 1.25 (95% CI=0.91, 1.72) for women only. Neither was statistically significant at the 95% level, but both were compatible with the combined relative risk of 1.19 (90% CI= 1.04,1.35.) There's that 90% confidence level again.

No mention was made of the fact that Shimizu *et al* found no increasing trend in risk with number of cigarettes smoked by the mother or paternal grandfather, nor that exposure to ETS of husband, father or children was not associated with risk.

**Hackshaw/Wald** Mention was made in the transcript (p 178) of the 1997 Hackshaw *et al*.<sup>42</sup> meta-analysis (actually a re-meta-analysis of an existing meta-analysis) of 37 published epidemiological studies of the risk of lung cancer. Careful reading of the report shows that "Data on the dose response relation between the number of cigarettes smoked by the husband and the risk of lung cancer was reported in 16 studies. That means that less than half of the studies reported a dose response trend. . ." Only 11 of the studies found a positive trend for duration of exposure. While the authors attempted to make it appear that only these studies had included exposure and dose data, this was not the case. In fact, a significant majority of the studies reported no trend for dose-response or dose-exposure. Once again, in an effort to 'prove' the point, the criteria for biological gradient has been failed. We are extremely disturbed at the misrepresentation of results.

**IARC/Boffetta** We may be mistaken that the IARC/Boffetta study are one in the same, since Boffetta has published other studies. However, frequent cross comments throughout the transcript led us to make this conclusion that they are one in the same. Dr. Bucher notes (transcript 179) that "There was no clear dose-response relationship reported in this study for cumulative exposure. . ." He goes on to *hope* that the higher OR with greater pack years might be taken as a dose-response trend. It is not. A trend must be monotonic. This one is not. Period.

In addition, the IARC multi center study reports its results as odds ratios rather than risk ratios -- another attempt to exaggerate what appears to be a non-existent association between ETS and lung cancer. Had the "raw" OR (1.35) been expressed as an RR, it would have been 1.17 (unadjusted). The IARC study goes on to correct the OR with an adjustment for age (by unspecified means) from 1.35 to 1.16. This is a factor 0.86 times lower than their raw value. If one presumes to apply a similar multiplicative correction to the raw RR (1.17), that would result in an adjusted relative risk of  $0.86 \times 1.17 = 1.01$ .

On p 234 of the transcript, Dr. Frederick enthuses about the editorial that accompanied the JNCI publication of IARC's multi center case control study of exposure to ETS. He refers to an editorial by Blot and McLaughlin, saying "they were two of the investigators in the study." *They were not involved in the study at all. William Blot and Joseph McLaughlin are affiliated with the International Epidemiology Institute in Rockville, Maryland.* Their "inescapable conclusion" is completely at odds with the actual results of the recent IARC study. This type of imprecision is typical of the entire proceeding. The IARC study showed NO statistically significant association for ETS and lung cancer and NO positive dose-response trend -- the bare minimum requirements for a positive assessment of risk.

### **FAILED: Strength, biological gradient, specificity.**

Dr. Zahn begins . . . "to set the stage, direct exposure to tobacco smoke is a known carcinogen." He cites animal data: ". . . condensate of sidestream smoke applied to skin, oral mucosa, or lung of experimental animals is carcinogenic." *ETS is not a condensate of sidestream smoke.* He points out that biomarkers indicate that exposure occurs. We have seen, however, in other transcript remarks that biomarker levels in ETS-exposed and non-exposed cases are substantially identical. This appears to be a non-issue.

Dr. Zahn also sees a "trend" in the one category of cases in the IARC/Boffetta study. A trend is not a one-point event.

**Willemsen** Dr. Zahn also comments about self-reported work exposures with a reference to Willemsen. The only material we have found from Willemsen are subjective surveys of aggravations of ETS in the workplace. A MedLine search for papers by Willemsen AND environmental tobacco smoke reveals only for papers:

- (1) Annoyance from environmental tobacco smoke and support for no-smoking policies at eight large Dutch workplaces. Willemsen MC, de Vries H, Genders R, *Tob Control* 1996 Summer 5:2 132-8, (2) Long-term effectiveness of two Dutch work site smoking cessation programs. Willemsen MC, de Vries H, van Breukelen G, Genders R *Health Educ Behav* 1998 Aug 25:4 418-35., (3) Saying "no" to environmental tobacco smoke: determinants of assertiveness among nonsmoking employees. Willemsen MC, de Vries H *Prev Med* 1996 Sep-Oct 25:5 575-82, (4) Determinants of intention to quit smoking among Dutch employees: the influence of the social environment. Willemsen MC,

Perhaps Dr. Zahn was thinking of another study which we were unable to find.

### **Various Biases**

**Diet** Dr. Zahn talks about adjustments for diet -- referencing Hackshaw, Nyberg and Boffetta. In re Hackshaw, only nine studies incorporated diet into their design -- in the form of fruit and vegetable intake. By ignoring dietary fat, the studies invalidated their confounder assessment. Intake of dietary fat is highly associated with lung cancer. "Dietary intake of saturated fat was the leading identified cause of lung cancer among lifetime nonsmokers and former smokers in Missouri,"<sup>43</sup>

Adenocarcinoma of the lung has been associated strongly with saturated fat intake (odds ratio [OR] = 2.3, 95 percent confidence interval [CI] = 1.2-4.4), whereas small-cell lung cancer has been associated with dietary cholesterol (OR = 2.8, CI = 1.1-7.5).<sup>44</sup>

Hackshaw writes that "most of the studies did not record data on diet, and we estimated its confounding effect indirectly. . . from a pooled regression analysis of studies of fruit and vegetable consumption." This is not adequate.

The IARC/Boffetta study discusses its subject and methods, ". . . (only) the centers from Germany, Sweden, Spain, The U.K. France, and one center from Italy collected information on dietary habits -- from which were derived indicators of intake of vegetables, fruits,  $\beta$ -carotene, total carotenoids, and retinol." This is not adequate.

We were unsure of which Nyberg study was under discussion. If it was the misclassification study of smoking status and lung cancer risk published in *Epidemiology* 1997 May 8:3 304-9, we found no discussion of dietary confounding in the abstract, but acknowledge that it could have been adequately considered in the study. We simply do not know.

Dr. Zahn concludes his remarks by stating unequivocally that the association (between ETS and lung cancer) is "certainly biologically plausible." We disagree, using Bradford Hill's criteria for biological plausibility.

### **FAILED: Plausibility, experimental evidence**



**Publication bias** Dr. Zahn states further that "there is also no evidence of publication bias against negative studies." We disagree. Bero reports in *JAMA*:

**CONCLUSIONS OF ARTICLES ON THE HEALTH EFFECTS OF ENVIRONMENTAL TOBACCO BY ARTICLE CLASSIFICATION. (Bero/Barnes in *JAMA*)**

	Peer-Reviewed, Original Articles with Statistics (n=49)	Symposium, Original Articles with Statistics (n=65)
Conclusion		
Positive	40	26
Negative	9	39

The majority of the symposia presentations are negative for association ETS and lung cancer (39 negative, 26 positive). We conclude that there is a strong bias toward publishing only positive conclusions are indicated by the majority of positive conclusions in published articles (40 positive, 9 negative). Submission bias should also be seriously considered.

### **Biased Publications?**

Interestingly, in *Tobacco Control* 1997 Spring 6:1 16-29, writing on the scientific quality of original research articles on environmental control, Bero and Barnes conclude "Article quality was not associated with either source of funding acknowledged or article conclusion in multivariate analysis," thus putting in doubt the unpleasant inferences that tobacco industry-funded studies are somehow inferior. We are curious as to how Bero and Barnes "controlled for sources of funding" without making an *a priori* judgement on the impact such sources might have.

We point out that a publication devoted to "tobacco control" with articles written by recipients of grants funded by anti-tobacco/smoking sources is hardly an exemplar of unbiased science.

### **Biased Research?**

"[I]n the current fervor of anti-smoking evangelism, what young scientists would want to risk their career and what older scientists would want to risk their reputation by doing anything that might be construed as support for the "bad guys" of the tobacco industry? What governmental agency would fund research in which the established "accepted" anti-smoking doctrines were threatened by a study proposed by someone -- an obviously deranged skeptic -- who wanted to do an unbiased, objective investigation?" asks one of the world's leading epidemiologists, Dr. Alvan Feinstein of Yale University Medical School.<sup>45</sup> Good question.

### **FAILED: Epidemiological Criteria -- Strength & Specificity.**

**Biological Plausibility** Dr. Yamasaki seems unclear on the criteria for biological plausibility, since he emphasizes that the components of MS and SS are similar as a basis for the biological plausibility for ETS and lung cancer, then notes that there is only one animal study (Witschi 1997) which is positive for ETS and lung cancer (this uses a high concentrated dose). He notes that there are two negative studies (Witschi and Finch), but somehow concludes that two negative studies and one (high concentration) positive study are somehow positive for association because the components of SS are "almost the same as those of MS."

Association by analogy fails the Hill criteria for plausibility for the simple reason that ETS is diffuse, dilute and undergoes chemical changes the minute it is exposed to air. The experimental evidence fails numerically, 2:1 -- without even taking the inappropriate concentrations of ETS to which the A/J mice were exposed.

### **FAILED: Biological Criteria -- Plausibility & Experimental Evidence**

#### **Temporality and coherence**

As regards temporality and coherence, we concede that exposure to ETS may have preceded lung cancer, however, the problems with selection and recall bias remain troublesome. In addition, "if the wives and children of smokers share in poor health habits or other factors that could contribute to illness, statistical associations found between disease and passive smoking could be incidental or misleading."<sup>46</sup> While the hypothesis that "if smoking causes cancer, then ETS must cause cancer" is logical on its surface, the facts simply do not support the hypothesis. We conclude that the test of coherence is failed, despite the fact that it may be "logical" the proposed relationship accords with the biology of the disease. The minuscule exposures involved, however, and the general misrepresentation of the nature of ETS, generally fail the test of coherence.

## 5. EPIDEMIOLOGY & META-ANALYSIS

In this section, we concentrate on two Biological, four Epidemiological and three Mixed Criteria set out by Bradford Hill<sup>47</sup>.

Biological Criteria include plausibility and experimental evidence. Epidemiological Criteria include strength, biological gradient, consistency and specificity. Mixed Criteria include coherence, temporality and analogy. Of the seven only one [temporality -- the exposure (ETS), even though not associated with the outcome (lung cancer in non-smokers and former smokers), did precede the event].

**Epidemiology is not an exact science.** Meta-analysis -- basically the application of mathematical "averaging" to disparate studies of a single hypothesis -- is fraught with problems. We have set out five basic rules which form the base for sound scientific inquiry as it relates to epidemiology and meta-analysis.

Of the published studies that deal with ETS in the workplace and lung cancer or heart disease risk, *only one* study (Fontham et al. 1994, "Environmental Tobacco Smoke and Lung Cancer in Nonsmoking Women," Journal of the American Medical Association, June 8, 1994) reports an overall statistically significant increased risk. But the reported risk is so small that, according to standards put forth by the National Cancer Institute (see below), it could be due simply to chance, statistical bias or effects of unknown confounding factors.

Further, Fontham's occupational risk estimates may be overstated. They appear to be confounded by uncontrolled and unrecorded non-occupational exposures to ETS. The authors acknowledge that exposures to household, social and workplace ETS may be concurrent. No adjustment for concurrent exposures was made in the analysis. Without this adjustment, the occupational risk estimate is inaccurate.<sup>48</sup>

It is our opinion that basic standards of sound science and statistical inference have been ignored in the study of ETS and its lack of association with cancer. It appears that listing ETS as a carcinogen was a pre-ordained goal and that conclusions and calculations have been willfully manipulated to make it appear that ETS is a human carcinogen.

We contend that the conclusion is false. We further contend that "rules of science" have been contorted in the case of ETS. Let us give you a wealth of examples:

## Rule No. 1: Relative risks of less than 2 are considered small.

While Hill does not directly address the strength of associations, a wealth of published literature supports the criteria that relative risks less than 100% (2.0) are weak and easily altered significantly by bias (deliberate or inadvertent) or confounding factors. Of the studies included in the original EPA report on ETS and lung cancer, more than 75% were statistically insignificant by these clear standards.

In a press release, dated October, 1994, on the topic of an article in the then current issue of the Journal of the National Cancer Institute, the National Cancer Institute clearly stated that: *"relative risks of less than 2 are considered small and are usually difficult to interpret. Such increases may be due to chance, statistical bias, or effects of confounding factors that are sometimes not evident."*<sup>49</sup>

An editorial accompanying the study under discussion, "Abortion and Possible Risk for Breast Cancer: Analysis and Inconsistencies," October 26, 1994, noted that a 50% *difference in risk "is small in epidemiologic terms and severely challenges our ability to distinguish if it reflects cause and effect or if it simply reflects bias."*

The International Agency for Research on Cancer (IARC), the scientific wing of the World Health Organization) has said: "Relative risks of less than 2.0 may readily reflect some unperceived bias or confounding factor." (ref: Breslow, N & Day, N, Statistical Methods in Cancer Research, Volume 1, 1980.)

"A significantly high HORs (hazard odds ratio) for the presence of two or more amine groups [HOR = 13.62, lower 95% limit = 1.82] is seen, whereas the odds ratio for one or more amine group *was not significant* [HOR = 5.1, lower 95% limit = 0.91]."<sup>50</sup>

"Unless a single risk factor for a disease outcome has a *relative risk over 5*... most (diseases) will not have a single risk factor."<sup>51</sup>

"If the confidence interval includes 1, then the difference in the effect of experimental and control treatment (or effect) is **not significant at conventional levels**  $P > 0.05$ )"

Egger et al, Meta-analysis principles and procedures. *BMJ* 1997; 315(7121):1533

"Of the 1,183 who received epidural, 97 women, or 8.2 percent had babies delivered by Caesarean section. Of the 1,186 who received narcotic pain injections, 67 women, or 5.6 percent, had C-sections. The difference was considered statistically insignificant." Application of the Center for Disease Control StatCalc program to these numbers reveals an OR of 1.4, 95% CI of 1.07-2.09. *Thus an OR of 1.49 is statistically insignificant.*<sup>52</sup>

"Using the dose-response curves that we calculated, the risk of breast cancer at alcohol intake of 24g (1 oz) of absolute alcohol daily (about two drinks daily) relative to nondrinkers was **1.4 (95% CI, 1.0-1.8)**

*in the case-control data and was 1.7 (95% CI, 1.2-2.2) in the follow-up data. We interpret these findings as not proof of causality...*"<sup>53</sup>

"The combined results from seven cohort studies demonstrated a *weak association* between breast cancer and the subsequent risk of colorectal cancer [pooled relative risk (RR) = 1.15; 95% CI = .99-1.31. *Pooled results from five cohort studies showed a similar (weak) risk (pooled RR = 1.10, 95% CI = 1.03-1.17.*"<sup>54</sup>

In a press release, dated October, 1994, on the topic of an article in the then current issue of the Journal of the National Cancer Institute, the National Cancer Institute clearly stated that: "*relative risks of less than 2 are considered small and are usually difficult to interpret. Such increases may be due to chance, statistical bias, or effects of confounding factors that are sometimes not evident.*"

"... pattern not consistent with dose response... reduced estimates to 1.40, 1.24, and 0.87, none of which differs significantly from 1.0."<sup>55</sup>

"No association was observed between high social class and the risk of testicular cancer (RR = 1.4, CI = 0.8-2.3)"<sup>56</sup>

"Because the magnitude of *association* between alcohol consumption and risk of colorectal cancer was *small* (1.10, 1.32, 1.07, 1.26, 1.11, 1.13), the findings regarding a causal role of alcohol were *inconclusive.*"<sup>57</sup>

"These results (RR 1.24, 1.30, 1.16) are consistent with other cohort studies that have shown *weak association or no association* between dietary fat and breast cancer."<sup>58</sup>

The USEPA report on ETS and lung cancer analyzes 31 epidemiologic studies of nonsmoking women married to smoking spouses, then combines the spousal smoking studies data into six statistical meta-analyses based on geographic origin. It analyzes high-exposure groups in the studies, conducts a trend analysis, and categorizes studies into four tiers based on their perceived utility for assessing a ETS/lung cancer association. The analysis uses one-tailed tests of significance and 90% confidence intervals, justifying this abrupt change from the previous 95% intervals by basing it on "... the *a priori* hypothesis that a positive association exists between exposure to ETS and lung cancer." Still, fewer than 25% of the studies show even a weak statistical association. See Figure 1.

We argue that the preponderance of evidence lies on the side of no or even negative association. Therefore, *narrowing the CI from 95% to 90% in midstream, so to speak, appears to be a tactic designed to torture the data to reveal positive results when no such results exist.*

Despite this tortuous reasoning, the relative risks calculated by the USEPA are a paltry 1.19. This barely suggests a very weak association.

### **FAILED: Epidemiological criteria for strength**

The classic ranking of relative risks, accepted by unbiased observers is as follows: <sup>59</sup>

Figure 3

INTERPRETING RELATIVE RISKS	
Relative Risk	Interpretation
Greater than 3	Strong association
Between 2 and 3	Weak association
Between 1 and 2	Very weak association
1	No association
Less than 1	Negative association

How does this weak 1.19 association (or even the 1.24 association expressed by Wald<sup>60</sup>) compare with other risks that have been reported for various exposures and diseases? Not very well. In fact, looking at Figure 4, it is clear that reported relative risks of less than 2.0 are uniformly discounted and that even risks reported as much higher can simply be discounted on the basis of common sense, much less tortured reasoning and statistical manipulation.

#### SAMPLE STATISTICAL ASSOCIATIONS

Exposure and disease	Reported relative risk (by size)
Environmental tobacco smoke and lung cancer	1.19
Consuming olive oil and breast cancer	1.25
Vasectomy and prostate cancer	1.3
Sedentary job and colon cancer	1.3
3 cups of coffee per week and premature death	1.3
Birth weight of 8+ pounds and breast cancer	1.3
Baldness in men under 55 and heart attack	1.4
Eating margarine every day and heart disease	1.5
Drinking tap water and miscarriage	1.5
Abortion and breast cancer	1.5
Eating yogurt and ovarian cancer	2
Drinking whole milk and lung cancer	2.14
Obesity in nonsmoking women and premature death	2.2
Eating red meat and advanced prostate cancer	2.6
Chlorinated drinking water and bladder cancer	2 to 4
Douching and cervical cancer	4
Workplace stress and colorectal cancer	5.5

Various studies as reported on Medline<sup>61</sup>

Figure 4

## Rule No. 2: Biological Plausibility has Precise Standards

### Physical & Chemical Properties<sup>62</sup>

Volume II contains page upon page of material designed to leave the impression that mainstream smoke and ETS are entirely similar -- or that ETS is somehow more dangerous than mainstream smoke. This really begs the imagination and somehow assumes that the highly diffuse content of ETS is somehow more concentrated.

ETS is highly diluted sidestream smoke produced by smoldering cigarettes, and from the small residues of mainstream smoke exhaled by active smokers. While the two substances are quite similar only in some respects, there *marked differences in chemical and physical composition and behavior*. All comprise gases (the gas phase), and small particles (the respirable suspended particles or RSP). These particles in turn may contain at various times, different amounts of water and other volatile components that may exchange with the gas phase.

Testing for carcinogenicity at near-toxic doses in rodents does not provide enough information to predict the excess number of human cancers that might occur at low-dose exposures. Testing at the maximum tolerated dose (MTD) frequently can cause chronic cell killing and consequent cell replacement (a risk factor for cancer that can be limited to high doses), and ignoring this effect in risk assessment greatly exaggerates the risks."

Gold *et al* Overview of analyses of the Carcinogenic Potency Database. In: Handbook of Carcinogenic Potency and Genotoxicity Databases (L.S. Gold & E. Zeiger, eds.). Boca Raton, FL: CRC Press, 1997

ETS and mainstream smoke may share some components, but their chemical and physical differences are substantial. Moreover, the presence of most ETS components can only be postulated because they are beyond material detection. The available evidence offers some limited opportunities to gauge ETS exposures and doses in relation to active main-stream smoking counterparts.

The major difference is that mainstream smoke is inhaled directly by smokers. Mainstream smoke is highly concentrated and confined to the moist environment of mouth, throat and lung. Its higher gas phase concentrations favor larger respirable particles that condense and retain more water and volatile compounds.

*ETS is over 100,000 times more diluted*, with much lower humidity and extremely low concentrations of volatiles<sup>63 64</sup>. Evaporation is faster from ETS particles; within fractions of a second from their generation-attain sizes 50-100 times smaller in mass and volume than in their mainstream counterparts. As ETS ages, it undergoes oxidative and photochemical transformations, polymerizations from loss of water and volatiles, reactions with other

environmental components, and other changes.

From several thousand components of main-stream smoke, Hoffman and Hecht have selected some 40 agents suspected of being carcinogenic on experimental animals.<sup>65</sup> In general, however, these agents have shown carcinogenicity in animal organs other than in the lungs, and only at doses much larger than even direct smokers attain.

Of the several thousand components identified in main-stream smoke, only perhaps 100 have been detected in side-stream smoke, due to extreme dilutions. Because of even greater dilutions only 20 have actually been identified (see Vol II, pp 1-3). Most ETS components are far below the sensitivity of current analytical capabilities.<sup>66</sup> The compilers of reports from the National Academy of Sciences,<sup>67</sup> the US Surgeon General<sup>68</sup>, and the Environmental Protection Agency have simply *inferred the presence of ETS components by proxy*, based on the composition of the highly diffuse sidestream smoke from which ETS derives.

### **Biomarkers**

A biomarker is a biomarker. A carcinogen is a carcinogen. Marking nicotine (which has never been implicated as a carcinogen) is a meaningless construct within the context of toxicology assessment. On page 236 of the transcript, Dr. Bingham thanks the public presenters saying, "... I am confounded -- I will use that word -- by the presentation on the biomarkers. That was troubling to me to see that, you know, *essentially they were the same number (of biomarkers) for the unexposed and the ETS exposed and then compare them with smokers*. I would have thought we would have seen some differences." Bingham then says he was "brought to reality" by Mr. Repace's comments on the need to "look at people who do not smoke like the -- is it the Seventh Day Adventists?" This is a totally absurd and unscientific proposition. *For a study to be valid, cases and controls should be as similar as possible.*

**FAILED: Biological criteria for plausibility.**

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### **Rule No. 3: Consistent Dose-Response over All Studies Is Required.**

Biological gradient (exposure or dose-response consistently exhibited over the range of the studies) is a critical factor in establishing cause and effect. There is *no clear pattern of dose/response in the majority of epidemiological studies tracking ETS and lung cancer* where quantity of exposure is measured.

Since Dr. Marks' comments on risk factors and overall study results were nearly identical to the conclusions we had already drawn, we also looked closely at this remarks on dose-response. We appreciated the care with which he made the distinction between trend analysis and true exposure-response analysis.

We had determined that only 16.6% of the papers used in the EPA report included the odds ratios necessary to conduct a trend analysis. His estimate was 17%. We had also determined that there needed to be a correlation between dose increase and odds or risk increase across the range of studies. Of the 24 trend tests reported by the EPA, only 11, or 41.6% showed any evidence of upward trend. Dr. Marks found that 67% of the tests for trend were non-monotonic. The discrepancy may be explained by the fact that we included multiple trend tests for single studies.

In either case, the exposure-response relationship is not exhibited over the majority of the studies.

Since we were unable to get the entire Cardenas, Fontham and Brownson studies, we are, based on our independent agreement with Dr. Marks, willing to accept his conclusion that 83% of their reported trends were non-monotonic.

### **Failed: Biological Gradient for Dose-Response Trend**

### **Rule No. 4: Epidemiology Is Easily Confounded**

We really cannot add anything substantial to Richard Peto's comments (see box) except, perhaps, to add that in the case of ETS confounding factors are rarely considered. When they are considered, they are not properly accounted for. Even when authors attempt to make

“(e)pidemiological observations... have serious disadvantages... (T)hey can seldom be made according to the strict requirements of experimental science and therefore may be open to a variety of interpretations. A particular factor may be associated with some disease merely because of its association with some other factor that causes the disease, or the association maybe an artifact due to some systematic bias in the information collection... It is commonly, but mistakenly, supposed the multiple regression, logistic regression, or various forms of standardization can routinely be used to answer the question: ‘Is the correlation of exposure (E) with disease (D) due to merely a common correlation of both with the same confounding factor (or factors) ?... Moreover, it is obvious that multiple regression cannot correct for important variables that have not been recorded at all... The disadvantages limit the value of observations in humans, but... until we know exactly how cancer is caused and how some factors are able to modify the effects of others, the need to observe imaginatively what actually happens in various different categories of people will remain...”

(Doll R, Peto R, *The causes of cancer*, JNCI 66:1192-1321, 1981. P. 1281)

adjustments for various factors, *the use of proxy variables instead of true risk factors is simply*

We have read as many full ETS studies as possible in the amount of time given to respond to the NTP’s proposal to classify ETS as a human carcinogen. In the absence of full studies, we have acquired abstracts and articles about the studies involved. We conclude that there is insufficient evidence of ETS carcinogenicity in more than 90% of the studies cited on the basis of inadequate attention to a wide variety of confounders:

- ▶ Family history, prior history of lung disease.
- ▶ Basic fitness/activity level of the subjects.
- ▶ Socioeconomic status.
- ▶ Diet and vitamin supplementation.
- ▶ Exposure to asbestos.
- ▶ Not a single study addresses anything even nearing the full range of confounders that are clearly important -- especially when the tortured statistics result in non-significant risk ratios.

## **FAILED: Epidemiological criteria for strength and specificity.**

### **Rule No. 5: Association is NOT causation.**

Relative risks are *only statistical associations*. They represent only an *apparent* relationship between exposure and disease. The relative risks association with ETS and lung cancer vary from extremely weak to non-existent.

There appears to be a willful corruption of the standards of interpreting relative risks in the conclusions reached by both the EPA and CEPA. Although the individual studies included assign the proper interpretation, the conclusions reached by these EPA/CEPA misrepresent the data overall. As for the IARC material, it concluded that, “*the available evidence (of a relationship between ETS and ANY cancer was insufficient to draw a conclusion.*” It is, however,

instructive to observe the degradation of standards applied to interpretation of relative risks as the process of "proving" a causal relationship between ETS and cancer is attempted. As regards nearly all published reports in ETS, the classic values for risk assessment have been lowered to an absurd level. Prior to the EPA's 1992 construct, one regularly expected to read types of statements that follow:

"The strength of association relates to causality. Relative risks of less than 2.0 may readily reflect some unperceived bias or confounding factor, those over 5.0 are unlikely to do so."

Breslow, Day *Statistical methods in cancer research. Vol 1: The analysis of case control studies.* IARC Sci Pub No 32, Lyon 1980. (P 36)

IARC monographs (Vol 38, p 280) states:

- ▶ "When analysis was confined to the 22 histologically verified cases, a ***marginally significant relative risk for pancreatic cancer of 2.0 was identified.***"
- ▶ "They estimated a ***non-significant relative risk of 1.3...***" (p 282).
- ▶ "In an American Cancer Society cohort study of 375,000 nonsmoking women (Garfinkel, 1981), ... the mortality ratios became 1.0, 1.4 and 1.0, respectively. ***Neither analysis showed any statistically significant increase in risk (for lung cancer from ETS).***" (p 303).

Other significant studies find ***no elevated cancer risk associated with workplace ETS:***

"In general, there was ***no elevated lung cancer risk*** associated with passive smoke exposure in the workplace. ..." (Brownson et al., 1992) "Passive Smoking and Lung Cancer in Nonsmoking Women" American Journal of Public Health, November 1992, Vol. 82, No. 11

"... an odds ratio of 0.91 ... indicating ***no evidence of an adverse effect*** of environmental tobacco smoke in the workplace." (Jannerich et al., 1990) "Lung Cancer and Exposure to Tobacco Smoke in the Household" New England Journal of Medicine, Sept. 6, 1990

"... the association with exposure to passive smoking at work was ***small and not statistically significant.***" Kalandidi et al., 1990 "Passive Smoking and Diet in the Etiology of Lung Cancer Among Non-Smokers" Cancer Causes and Control, 1, 15-21, 1990

"***No association was observed*** between the risk of lung cancer and smoking of husband or passive smoke exposure at work." Shimizu et al., 1988 "A Case-Control Study of Lung Cancer in Nonsmoking Women" Tohoku J. Exp. Med., 154:389-397, 1988

"... ***no statistically significant increase in risk*** associated with exposure to environmental tobacco smoke at work or during social activities...." Stockwell et al., 1992 "Environmental

Tobacco Smoke and Lung Cancer Risk in Nonsmoking Women" Journal of the National Cancer Institute, 84:1417-1422, 1992

***"There was no association*** between exposure to ETS at the workplace and risk of lung cancer."  
Zaridze et al., 1998

These researchers carefully adhered to the sound principles of interpreting relative risks. The fact that their reports were deliberately misrepresented as "positive" findings is an appalling corruption of accepted scientific and statistical standards.

We have included a re-sampling of Brownson and Fontham in this public comment (see immediately following pages). We were able to find a copy of an oral presentation by William J. Butler, Ph.D., Environmental Risk Analysis, Inc., San Mateo, CA, as part of the CEPA proceedings. It appears that this is the same Mr. Butler whose comments were apparently disregarded by the NTP subcommittee. We find his re-analysis to be sound.

### **FAILED: Epidemiological criteria for consistency.**

#### **A fresh look at Brownson and Fontham.**

Since the Brownson and Fontham (1994) studies received such weight in both the EPA and CEPA documentation, we searched for raw data (unsuccessfully) and for public commentary on the studies. We were fortunate to find the work of William Butler, PhD., one of the public presenters at the NTP sub-committee hearings whose work was apparently ignored by the sub-committee. We believe his comments are quite valid.

Butler, observes that, when re-analyzed<sup>69</sup>, according to accepted epidemiologic and statistical standards, two of the major studies cited in the CEPA report (Brownson and Fontham) show no association between ETS and lung cancer. The inconsistency between the stated conclusions in these reports and the patterns of association present in their data are marked.

#### **Re-Analysis of the Raw Data of the Brownson Study Lifetime Never Smokers, All Respondents and Self-Respondents Spousal Smoking**

			All Respondents		
			(Brownson et al., 1992, Table 2)	Self-Respondents	

Spousal Smoking	No. of Contr ols	No. of Cases	OR*	95% CI	No. of Cases	OR*	95% CI
Never	568	213	1.0	--	80	1.0	--
Ever	598	218	1.0	0.8,1.2	74	0.9	0.6,1.2
Cigarette pack-years							
0	568	213	1.0	--	80	1.0	--
0< <15	128	32	0.7	0.5,1.1	18	1.0	0.6,1.7
15< <40	200	54	0.7	0.5,1.0	20	0.7	0.4,1.2
40 <	216	110	1.3	1.0,1.7	32	1.0	0.6,1.6

\* Adjusted for age and history of previous lung disease

The two odds ratios presented in the article by Brownson et al that mislead USEPA and CEPA are presented in the set of columns for All Respondents; i.e., 1.3 for “Highest Exposure Category v Never.” This OR is the only possible result in Brownson et al. To support their stated conclusion that “Our and other recent studies suggest a small but consistent increased risk of lung cancer from passive smoking.” However, this assertion is NOT supported by or consistent with the results of the more valid analyses that include only self-respondents.

Using raw data obtained from NCI, and the preferred analysis of self-respondents, which avoids the potential bias introduced by the less reliable and less valid information from surrogate respondents who are less knowledgeable about the subject’s actual exposures. The preference for analyses only for self-respondents is *standard and accepted, even preferred epidemiologic practice*. Brownson et al. reported that they performed statistical analyses only for self-respondents, but they did NOT provide the quantitative results from those analyses.

As can be seen in the set of columns for self-respondents, there is NO association between lung cancer and “Ever v Never” exposure; i.e., the OR is 0.9. There is NO pattern of association between lung cancer and categories of ETS exposure; i.e., all ORs for exposure categories are equal to or less than 1.0 for self-respondents.

**Re-Analysis of the Raw Data of the Brownson Study,  
Lifetime Never Smokers, Cases Partitioned by Type of Interview:  
Occupational ETS Exposure\***

	Self-Respondents			Surrogate-Respondents			
Occupational ETS Exposure	No. of Contr ols	No. of Cases	OR**	95% CI	No. of Cases	OR**	95% CI
Never	560	66	1.0	—	85	1.0	—
Ever	434	59	1.1	0.8,1.7	56	0.9	0.6,1.3

\* Among women who worked outside the home\*\* Adjusted for age and history of previous lung disease.

Looking at raw data from an objective standpoint, with a keen eye for the residual biases mentioned by Egger et al, results in a null association. It is extremely important for both case and control groups to be as “clean” as possible of confounding factors -- and for cases and controls to be as similar as possible. These are basic tenets of sound science and are particularly critical in the area of meta-analysis of epidemiologic studies.

We simply cannot ignore, for the sake of an apparent desire to list ETS as a carcinogen, the fact that not only to a vast majority of studies show no statistically significant association, but that one of the largest studies (Fontham), which has received much attention as “proving” the association between ETS and cancer, has essentially null results when re-analyzed to discount the multiplicative effect of combining exposure groups.

***The possibility that the Fontham results are null cannot be ignored.***

**Data from Fontham et al., (1994, Table 8),  
Crude Association of Lung Cancer with ETS Exposure,  
Restricted to Self-Respondents**

<b>(a) Case Control</b>								
<b>Adult ETS Exposure</b>			<b>Childhood ETS Exposure</b>					
			<b>No</b>			<b>Yes</b>		
<b>No</b>			<b>23/71</b>			<b>5/44</b>		
<b>Yes</b>			<b>118/364</b>			<b>235/724</b>		
<b>(b) ORs &amp; 95% CI</b>								
<b>Adult ETS Exposure</b>			<b>Childhood ETS Exposure</b>					
			<b>No</b>			<b>Yes</b>		
<b>No</b>			<b>1.00 Baseline</b>			<b>0.35 (0.12, 0.99)</b>		
<b>Yes</b>			<b>1.00 (0.60, 1.67)</b>			<b>1.00 (0.61, 1.64)</b>		

The Fontham study examined the joint exposure to childhood and adult ETS exposure. The CEPA report cites the results of Fontham's analysis of that joint exposure as presented in Table 8 of the article of Fontham et al. CEPA was remiss in not addressing the manner in which Fontham et al. conducted and presented those analyses because Fontham et al. *did not acknowledge* the presence of a statistical interaction that supports the absence of an association between ETS and lung cancer.

Re-analysis of the data from Table 8 of Fontham et al. (1994) on the joint exposure to ETS during childhood and adulthood using a single baseline group (that is, those with neither childhood nor adult ETS exposure) for all combinations of exposure achieves a markedly different conclusion. (The use of a single baseline group is recommended in standard epidemiologic textbooks such as Kleinbaum, Kupper and Morgenstern; Breslow and Day; Schlesselman; and others.)

Entries in the first table indicate the number of cases and controls for each combination of childhood and adult ETS exposure as presented in Table 8 of Fontham et al. The baseline group of women with neither childhood nor adult ETS exposure is in the upper left hand corner.

Based on this single baseline group, the odds ratios for the two categories of women with adult exposure equal 1.0; that is, no association between adult ETS exposure and lung cancer --

regardless of whether or not the women had childhood ETS exposure.

Fontham incorrectly interprets these data to indicate that adult ETS exposure is associated with higher lung cancer risk and that the elevations in risk for women exposed during childhood were twice as high as those of women not exposed during childhood. Specifically, using Fontham's approach of stratum-specific baseline groups, one obtains an odds ratio =  $2.86 = 1/0.35$  for adult ETS exposure among those with childhood ETS exposure and an odds ratio of 1.00 among those with no childhood ETS exposure. Fontham incorrectly interprets this first odds ratio to indicate that those with both childhood and adult ETS exposure are at about twice the risk of lung cancer relative to those with adult but no childhood ETS exposure.

However, it is clear from the analyses presented here (and *not* presented in Fontham et al.) that this interpretation is wrong. The increased odds ratio for those with both childhood and adult ETS exposure results not from increased risk associated with both exposures but from a significantly lower risk among those with childhood but no adult ETS exposure. This is an unexpected finding that, most likely, reflects a shortcoming of the Fontham data set due to bias in sample selection or data collection.

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The data presented here clearly indicate that there is no increased risk of lung cancer associated with adult or childhood ETS exposure, and any analyses that implies such an association distorts the patterns present in this data set.

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## SUMMARY OF FINDINGS

<b>Brownson Study:</b>	<b>No Association of Lung Cancer Risk with Spousal of Workplace ETS. Exposure Among Self-Respondents Who Are Lifetime Never Smokers</b>
<b>Fontham Study:</b>	<b>No Association of Lung Cancer Risk with Adult ETS Exposure During Childhood.</b>
<b>U.S. EPA (1992):</b>	<b>The two largest U.S. studies were published post-1991 and generate results consistent with each other and <i>contrary</i> to U.S. EPA's conclusion that ETS is a carcinogen.</b>
<b>CEPA (1997):</b>	<b>The CEPA report repeats the same misleading conclusions contained in the USEPA report. Both are based upon inaccurate calculations and the conclusions are NOT support by the data.</b>

In summary, the two largest U.S. epidemiologic studies of ETS and lung cancer were published after the U.S. EPA's risk assessment. These two studies benefit from methodologies designed to address, at least partially, some of the shortcomings of all the previous research. The data from these two studies are in agreement: **There is no association between lung cancer and adult ETS exposure, a finding that contradicts the stated conclusions of each study.** These discrepancies demonstrate the errors that can occur if one relies solely on published results and



conclusions. *Data from the two largest U.S. epidemiologic studies are not consistent with U.S. EPA's conclusion that ETS is a lung carcinogen or with CEPA's conclusion that post-1991 epidemiologic studies support a casual relationship between ETS and lung cancer.*

**FAILED: Analogy, plausibility, strength, specificity.**

## **Rule No. 6: Publication Bias must be accurately factored.**

One of the major flaws in using meta-analysis is the potential for "publication bias." Studies for a meta-analysis are usually selected via literature review. There is an inherent bias here since studies may tend to be published far more readily if they show positive statistical significance or are judged to have more reader interest in terms of the influence of their outcomes on the professional field involved, or, sadly, their potential to generate publicity and increased circulation for the publication.

G.V. Glass, who introduced the concept of meta-analysis in the social sciences, noted recently<sup>70</sup> that "the potential for publication bias concerns us because ... if positive results get published more, then the risk of adopting ineffective and even harmful practices (or policies, ed. note) is greater." The problems of publication are well documented and only scantily addressed in the NTP discussion. Indeed, the pro-listing presentation on publication bias largely discounted the possibility after failing to find any negative studies.

The public presenter on the same topic (LeVois) discussed actual studies that had been located, concluding that "... it is important to note that in our study we were able to find three very important studies that had not been reported. Two American Cancer Society studies and the National Mortality Follow Back were all three null (for association of ETS and cancer), very large studies and available to scientists to review." He continues: "We found some studies. I think it is a lot more significant to find unreported studies than not to." (Transcript p 229) We agree.

### **Unpublished or not submitted?**

"At one level, it simply refers to a greater likelihood of studies with statistically significant results being submitted and published in the literature. Researchers' decisions not to submit nonsignificant results are likely to be based on a belief that nonsignificant findings are less interesting than statistically significant ones, and also that journal editors have been shown to be more likely to reject null results."<sup>71</sup>

Completing a full search for published literature can be daunting. Reasons for failing to do so can range from the loss of authors from the academic system to private industry, studies being suppressed by vested interests, on a systematic bias against authors of non-English speaking languages being published in Western publications. "The variety of reasons for studies being missed does show the difficulty of completing a full search of all known results in any specific area. ... The impact of meta-analysis in medical and epidemiological areas is evident in the

following table, derived from a recent (1998) search of the Medline database. It is interesting to note the parallel, yet lagged, advent of the literature on publication bias.

**Results of Medline Search for Meta-Analyses & Articles on Publication Bias<sup>72</sup>**

Years	Meta-analysis	Publication Bias
1966-1974	0	0
1975-1979	2	1
1980-1984	46	0
1985-1989	428	19
1990-1992	1259	30
1993-1994	1182	66
1995-1997	2172	95

Publication bias is a major threat to the validity of meta-analysis. Obtaining and including data from unpublished studies, however, is not always possible. There are ways to account for publication bias. Funnel plots and simple 'trim and fill' techniques can estimate and adjust for the numbers and outcomes of such missing studies. Both supply consistent results of reducing the perceived risk by as much as 30%.

"Studies for a meta-analysis are usually collected through a review of the literature. Since insignificant studies are, by the very nature of the scientific process, published less frequently (if at all), such a process is inherently subject to bias introduced from being based on only one part of the real population.

"This problem has recently received considerable notoriety in the debate on passive smoking (ETS). . . . No attempt (to account for all published studies, and if possible unpublished studies) was made by the EPA. . . .

"Our analysis indicates that world-wide, there may be around ten possible missing negative studies, and a similar number of missing insignificant positive studies. After allowing for this, . . . the 95% posterior credibility interval for relative risk is shifted downward towards the null hypothesis of no effect; more importantly, perhaps, the actual estimate of excess risk is cut by approximately one-third."<sup>73</sup>

***"CONCLUSION.--There is a statistically significant association between significant results and publication."***<sup>74</sup>

In an excellent series of articles published in the *British Medical Journal*, Matthias Egger and George Davey Smith, et al, exhaustively covered the many problems faced by meta-analysts regarding publication bias. It is unclear to us that any of these factors have been adequately accounted for by EPA, CEPA, IARC or NTP. A single article by Bero (co-author of a number of

anti-smoking studies) is hardly the final word on publication bias. Indeed, the referenced article appeared to be an example of scientific bias on the part of Bero.

<b>META-ANALYSIS: SPURIOUS PRECISION -- Association is not cause</b>
Confounding and selection bias often distort the findings from observational studies
There is a danger that meta-analyses of observational data produce very precise but equally spurious results
The statistical combination of data should therefore not be a prominent component of reviews of observational studies
More is gained by carefully examining possible sources of heterogeneity between the results from observational studies
Residual confounding arises when a confounding factor cannot be measured with sufficient precision -- which often occurs in epidemiological studies.
Studies can yield estimates of association which may deviate from true underlying relationships.
Analysts may well be simply be producing tight confidence intervals around spurious results.
An important criterion supporting causality of associations is a dose-response relationship.
Implausibility of results rarely protects from reaching misleading claims.

Egger et al. BMJ, article #5 of 6.

## **FAILED: Epidemiological criteria for strength, specificity**

### **Industry v Government/Institutional Bias**

Much was made in the NTP transcript of an article in *JAMA* by Barnes and Bero who hypothesized *a priori* that the review articles concluding that ETS exposure is not associated with significant health outcomes would be of inferior quality and more likely to be written by "tobacco industry-affiliated" authors. Barnes and Bero defined this affiliation as follows: The authors must have received funding from the tobacco industry or submitted a statement on behalf of the tobacco industry regarding the EPA's risk assessment on passive smoking. Apparently they felt that any scientist foolish enough to point out that research does NOT show sufficient evidence that ETS is a carcinogen must somehow have been co-opted by some institutional phantom.

The implication is that some knowledge should be forbidden the light of day because of the source of its funding. We find this offensive and disturbing

The tobacco industry's interest in the basic science and epidemiology of ETS may be a vested interest, but the published results should be judged on their own merits -- not on their "politically incorrect" results. When scrutiny of research -- both during peer review and post-publication -- is objective and scientific it is valuable. NTP's thinly veiled hostility toward presenters finding no convincing evidence of ETS carcinogenicity is unacceptable. We found the presentations of varying quality, but were generally impressed with their factual and substantive nature. Not so several of the "pro-listing" presentations (notably Repace), which were quite subjective and

included not a whiff of scientific objectivity or rigor. We mention elsewhere the alarming proposal that 7<sup>th</sup> Day Adventists would be an ideal control group to “prove” the danger of ETS. Since the similarity of control and case groups is a fundamental rule of scientific study, we simply cannot understand how this absurd suggestion was given any credence at all.

“... the integrity of research sponsored by governmental or other private organizations is rarely questioned. Ignoring the possibility that the granting agencies may have specific agendas for the research they sponsor, there are substantial pressures on scientists to publish and a well-known bias against publication of negative data.”

Letter, *JAMA*, 1998;280:1141

“The quality of published science funded from any private or government source speaks for itself, without coaching from the sidelines on matters of political correctness. . . notably, their analysis of 106 review articles revealed that articles that concluded ETS health effects insignificant were of no less quality than those that judge ETS to be harmful. Nor were these articles less likely to have been peer reviewed than articles having conclusions more to the liking of Barnes and Bero.”

Letter, *JAMA*, 1998;280:1142

We applaud all of the private presenters at the NTP subcommittee meeting for having the courage to face this witchfinding attitude. Bero replies to correspondence regarding her article, “Every independent scientific body that has reviewed the scientific evidence has concluded that exposure to passive smoke is harmful to health” -- citing her own article as a reference. This challenged us to take a look at these putatively ‘independent’ scientific bodies. We refer you to Section \_\_ of this report: Scientific Misconduct.

After researching the original risk assessment proceedings of the EPA and becoming depressingly familiar with the proceedings of the NTP assessment process under discussion, *we conclude that the so-called “independent scientific bodies” were not independent at all*, but rather were pressured by a wide variety political and procedural forces to cast (quite reluctantly in several cases) their weight on the side of ETS as a carcinogen.

After reviewing the NTP materials forwarded to us, as well as the source materials and complete documents we could acquire during the response period, *we conclude that government and institutional bias far exceeds industry bias in the issue of ETS.*

**FAILED: Strength, specificity**

## 6. SPECIAL COMMENTS

### Seventh Day Adventists: An Totally Unscientific Control.

In the transcript, Mr. Repace posits that using Seventh Day Adventists (SDAs) as a control group for ETS exposure would make risk assessment more accurate. It is here that he extrapolates a potential relative risk of 2.5. This figure is totally unsubstantiated. What is more, it is based on a perversion of sound science. Note well the following:

“...treatment and control groups (should be) similar for all the factors that determine the clinical outcomes of interest save one: whether they received the experimental therapy (or were exposed to a risk factor.) Investigators provide this reassurance when they display the "entry" or "baseline" prognostic features of the treatment and control patients. Although we never will know whether similarity exists for the unknown factors, we are reassured when the known prognostic factors are nicely balanced.”<sup>75</sup>

The SDAs avoid “unclean” meats (largely pork and shellfish), abstain from alcoholic drinks, smoking and nonmedical drug use. A large proportion of SDAs practice vegetarianism. *This is hardly typical of the general population.*

Reputable science demands that *cases and controls should be as exactly alike as possible, except on the exposure issue.* Comparing the general population to SDAs is not a good comparison.

“...treatment and control groups (should be) similar for all the factors that determine the clinical outcomes of interest save one: whether they received the experimental therapy (or were exposed to a risk factor.) Investigators provide this reassurance when they display the "entry" or "baseline" prognostic features of the treatment and control patients. Although we never will know whether similarity exists for the unknown factors, we are reassured when the known prognostic factors are nicely balanced.”

Gordon Guyatt, MD; Roman Jaeschke, MD; Nancy Heddle, MSc; Deborah Cook, MD; Harry Shannon, PhD; Stephen Walter, PhD: Basic statistics for Clinicians, Canadian Medical Association, 1995.

*Comparing 7<sup>th</sup> Day Adventists to the general population would result in less accurate, rather than more accurate results.*

We absolutely cannot understand how this untested and unsound comparison, along with Repace’s unsupported contention that RRs of 2.5 are somehow more real than the actual, statistically weak associations reported in published literature came to be considered in by the NTP subcommittee.

Yet, on page 240 of the transcript, Dr. Medinsky says, “I just want to make a comment on the

epidemiology. I guess *the relative risks in this for ETS are from my perspective quite low*. And that was -- that was troubling me this entire time. And I think James Repace's comments regarding the Seventh Day Adventists and if we could actually get a control group that was truly unexposed that the relative risk would go up *comforted* me quite a bit."

"Comforted?" We repeat: Cases and controls should be exactly alike, except on the exposure issue.

The SDAs avoid "unclean" meats (largely pork and shellfish), abstain from alcoholic drinks, smoking and nonmedical drug use. A large proportion of SDAs practice vegetarianism. This is hardly typical of the general population.

We cannot emphasize strongly enough that this type of unscientific projection -- a rather bizarre red herring thrown into the subcommittee's deliberations -- is scientifically unsupportable. Yet Repace's comments are actually given importance, no less credence, in the final decision making process. This issue alone is enough to undermine any

credibility on the part of NTP's decision to list ETS as a carcinogen. The addition of other flaws, misrepresentations and misinterpretations combine to make this decision highly suspect -- both scientifically and morally.

In our opinion, the subcommittee should have rejected out of hand, this strange contention that SDAs are any kind of acceptable control group for a study of anything other than another group of Seventh Day Adventists.

Reputable science demands that *cases and controls should be exactly alike*, except on the exposure issue. Comparing the general population to SDAs is not a good comparison. Using this type of control group would result in less accurate, rather than more accurate results

**FAILED: Basic standards for reputable science.**

## 7. GENERAL COMMENTS

### **Rush to Judgement: A disturbing pattern in ETS analysis.**

On page 238 of the transcript, Dr. Mirer states, "I don't see how we can take into account unpublished data that is presented here (by those arguing *against* listing ETS) at the last minute without -- I mean, *it is true we have had copies in advance, but it is simply not possible to evaluate that kind of data in the face of a proceeding of this magnitude and rapidity.*"

Why then are Repace's unsubstantiated, off-the-cuff comments given any consideration? And why was the process rushed?

Mirer goes on to say, "I hope when we get to diesel we will get the same *generous interpretation of epidemiology that we are getting here.*" Chairman Brown admonishes Mirer, saying, "Don't lobby your cause."

It would appear that the rapidity of the process was designed to avoid valid scientific scrutiny and that some members of the subcommittee clearly had pre-conceived results in mind and were willing to trade sound science for the desired vote on listing ETS and/or diesel fuel.

This is unsupportable. It is unscientific. It is unacceptable. And it may well be illegal.

### **Witchfinding**

The Puritans in the New England colonies employed hunters to rid them of witches. The hunters engaged witchfinders to gather evidence against purported witches -- or rather, to manufacture the evidence. They were paid commissions on the witches they managed to "expose."

It is our opinion that NTP, the USEPA and CEPA have systematically engaged in a modern day version of "witchfinding" as regards environmental tobacco smoke. First, the USEPA appears to have concluded that ETS causes cancer *prior to investigation* -- it excluded studies that reported negative correlations and altered in midstream a critical statistical standard (confidence interval) in order to artificially create the appearance of risk. Second, CEPA has taken the USEPA's unwarranted conclusion and further misrepresented epidemiologic studies to bolster the conclusion. Finally, the National Toxicology Program's Report on Carcinogenicity Subcommittee has willfully ignored sound evidence (see Gori, Brown, and other outside presenters), accorded unwarranted value to highly questionable and unsubstantiated conjecture (see Repace, 7<sup>th</sup> Day Adventists) and, apparently, traded votes of listing approval to advocates of one politically motivated program in return for votes for other politically motivated programs (see Mirer, Chairman Brown).

## Misrepresentation of facts

On p 203 of the transcript, Mr. Repace says that "EPA's 1992 report was reviewed by an outside science advisory board of 18 independent experts who unanimously endorsed the report, heard the tobacco industry's comments, and rejected them." Our research shows that this is, to put it kindly, a misleading statement. We have found significant evidence that a number of members of the *SAB did not approve of much of the methodology of the report*. We have found that the industry was not involved in the initial process of assessing ETS as a carcinogen. This is an important distinction. It appears to us that the entire issue of the carcinogenicity of ETS has been what can only be called a "railroad" process. One track. One destination. Only one permissible conclusion.

Intrigued by Mr. Repace's statement "I commissioned the EPA study back in 1987..." (Transcript p 202), we took a closer look at this involvement in the ETS-as-human-carcinogen process.

According to Congressional testimony by the Honorable Thomas J. Bliley, Jr., at the House Committee on Energy and Commerce Health and Environment Subcommittee meeting, July 21, 1993, "EPA's policy of promoting restrictions on smoking seems to have begun with James L. Repace, an 'environmental protection specialist' in EPA's Indoor Air Division. Mr. Bliley's testimony revealed a pattern of conduct and association that causes us to seriously question the scientific merit of Mr. Repace's position.

'In 1980, even before the first major ETS health claims appeared in the scientific literature, Repace wrote with A.H. Lowrey an article reporting on particulate matter in the air of various environments such as bars, restaurants and bingo parlors, without distinguishing whether those particulates were from ETS or some other substance or activity. The only "office" measurements made by Repace were in an experimental, enclosed room in which thirty-two cigarettes were smoked in less than one hour, generating ETS levels grossly in excess of those encountered in the real world. Subsequent research has discredited both the methodology and conclusions of the 1980 Repace study. On the basis of these observations, however, the article claimed that 'indoor air pollution from tobacco smoke presents a serious risk to the health of nonsmokers \* \* \* [that] deserves as much attention as outdoor air pollution.'

"A few years later, Repace published (again with A.H. Lowrey) an article purporting to show that ETS was riskier than "all regulated industrial emissions combined." This second article by Repace and Lowrey, which represented a crude attempt at quantitative risk assessment, has been roundly criticized by both government and private sector scientists.

"Repace's extensive work with political advocacy organizations such as the Group Against Smoke Pollution ("GASP") and Action on Smoking and Health ("ASH") and his private and professional focus on smoking raise questions about Mr. Repace's ability to evaluate indoor air issues in a balanced manner. Since the 1970s, Mr. Repace also has been appearing as a paid witness in numerous lawsuits and testifying before various legislative bodies to support governmental restrictions on smoking."



This is especially repugnant given the thinly veiled aspersions cast on public presenters at the NTP sub-committee hearings on ETS.

Mr. Repace states (Transcript p 203) that "EPA's 1992 report was reviewed by an outside science advisory board of 18 independent experts who unanimously endorsed the report." Mr. Repace freely admits prejudging secondhand smoke (7/22/98 USA Today), stating that, "We had enough information to make policy... and that EPA only sought to quantify the link in its 1993(sic) report." But hazard identification is the first step of a risk assessment. *Repace's comments indicate that issue wasn't open for discussion during the risk assessment process.* Even *USA Today*, hardly an expert in risk assessment methods, was sharp enough to note that, "Curiously, the final EPA risk assessment relied mainly on the Fontham study, not issued even in preliminary form until 1991. The final Fontham study wasn't published until June 1994, more than 18 months after the EPA risk assessment was released." We have discussed a re-analysis of Fontham that eliminates overlapping categories and reduces the adjusted relative risk to 1.0 -- that is, no risk at all.

Mr. Bliley points out that "...the EPA Science Advisory Board is intended to serve as an independent review body composed of impartial experts from outside the Agency. Its function is to ensure Agency accountability and integrity in the use of science. In addition to the seven standing members of the SAB's Indoor Air Quality and Total Human Exposure Committee, the decision was made at EPA to select nine scientists to serve in an *ad hoc* capacity on the panel that was to review the draft ETS risk assessment and policy guide. Because they were to review work that had been developed and put forward by Agency staff and others with vocal anti-smoking records, their ability to conduct a fully objective critique was essential. . . Unfortunately, the panel ultimately was not balanced . . . eight of the fifteen panel members were themselves responsible for scientific studies relied upon in the first or second drafts of the risk assessment -- hardly the type of circumstances that ensure independent evaluation."

We were struck by the similarities between the NTP sub-committee hearing and the SAB panel meeting on December 4-5, 1990, which was, according to Mr. Bliley, "... conducted in a manner that effectively prevented scientific viewpoints critical of the two draft ETS documents from being given anything resembling a full and fair hearing. Less than two hours were allowed for presentations by scientists critical of the report. Certain attendees who had personally requested time from the Chairman were foreclosed from speaking under the agenda that had been formulated. The input of several critical points of view was lost, as well as the opportunity for the panel to ask questions and to conduct a dialogue with other scientists. In contrast, twice as much time was given to anti-smoking organizations. Although there certainly was enough time to accommodate all who had asked to speak, several scientists who had expressed doubts about the risk assessment and policy guide were denied the chance. No explanation was given for the failure to accommodate these speakers or why the SAB hearing was conducted with such rigidity. Most SAB review panels are conducted in an open and collegial manner that encourages vigorous discussion of all competing scientific viewpoints.

"Two of the ETS panel members who agreed to review the report did not even attend the first day of the meeting, which was the only time reserved for public comment. Other panel members

openly admitted that they had not read any of the written submissions. The panel members did not address or acknowledge the many public comments in their written reviews.

"No presentations were permitted on the risk assessment chapter dealing with the respiratory health of children. Without providing any opportunity for public comment, EPA had transmitted to the SAB a new "draft report with a detailed description and analysis of 26 studies" on childhood exposure to ETS. Not surprisingly, the document failed to discuss any studies that did not support EPA's preferred conclusions. By inserting it at the last moment and preventing public discussion of the topic at the hearing, meaningful public scrutiny of the Agency's conclusion was excluded.

"The negative perception created by the SAB was heightened by the *Chairman's summary remarks and statements by him and others to the press after the panel adjourned, misleadingly suggesting that the panel had reached a "consensus" on the classification of ETS as a human carcinogen*. As the transcript of the meeting shows, there was no such "consensus." Several panel members criticized the draft in key respects. Dr. Jeffrey Kabat, for example, repeatedly questioned important aspects of the methodology used in the draft as well as its treatment of specific studies before concluding that classifying ETS as a Group A carcinogen could be "rash". Dr. Kabat stated that 'the observations on nonsmokers that have been made so far are compatible with either an increased risk from passive smoking or an absence of risk or I would say that with a risk that's so small that maybe it's not -- you can't measure it with certainty'. *Others on the panel expressed similar reservations about the draft's conclusions.*

"The advisory panel also did not consider a number of pertinent studies, including a study by one of its own members, Dr. William Blot of the National Cancer Institute. Dr. Blot had served, along with Dr. Wu-Williams, as one of the principal investigators on one of the largest studies ever conducted on ETS and lung cancer among nonsmokers. However, the new study was not discussed by the panel, even though the study had been accepted for publication in the British Journal of Cancer before the panel met. Amazingly, Dr. Blot himself did not mention the study, which reported no health risks from ETS.

"After the panel meeting, (there was a) press conference to announce the conclusion that ETS 'should be classified as a Class A carcinogen.' The impropriety of a supposedly impartial scientific expert attempting to frighten the public on the basis of an incomplete and unsupported document speaks for itself. But Dr. Lippmann compounded this breach by misrepresenting the panel's conclusions concerning the strength of the evidence. Among other remarks, Lippmann stated that "if anything, [the evidence] suggests that it is more potent than we had thought" (Evidence Shows That Tobacco Smoke Causes Cancer, Head of EPA Panel Says, Bureau of National Affairs, Daily Report for Executives, December 7, 1990, p. A 8). Perhaps realizing that he had gone too far, Lippmann subsequently tried to qualify his remarks but succeeded only in being inconsistent. *"[T]his is a classic case where the evidence is not all that strong."* Nonetheless, Lippmann asserted, the "weight of the evidence" supports the risk assessment's conclusions (Passive Smoke A Cause of Cancer, Panel Concludes, The Washington Post, December 6, 1990, p. A 9).

## SAB Executive Committee Meeting, April 1991

"Dr. Lippmann presented the SAB panel's report to the SAB's Executive Committee meeting in April 1991. This report was curious for several reasons. First, the SAB concluded that the worldwide epidemiologic data on ETS were too weak and inconclusive to support the draft risk assessment's conclusion that ETS is a cause of lung cancer in nonsmokers. In addition, the panel did not endorse the Agency's quantitative lung cancer analysis, noting that the 'real' number 'may be greater or less than the number EPA cites.'

"After concluding that the rationale underlying the EPA staff's conclusions about lung cancer could not be sustained, however, the SAB could not bring itself to take the logical, if politically unpalatable, next step and reject EPA's conclusions regarding ETS and lung cancer among nonsmokers. Instead, the SAB endorsed the conclusion that ETS is a "Group A" carcinogen while taking the extraordinary step of urging the EPA staff to attempt to "make the case" against ETS based on extrapolation from data concerning active smoking. In essence, *the Agency was being encouraged to do the science backwards -- to maintain its conclusion while going about the task of finding support for it.*

"Not surprisingly, the SAB report did not acknowledge that EPA had largely ignored its own 'Guidelines for Carcinogen Risk Assessment,' 51 Fed. Reg. 3394 (September 24, 1986), in order to reach its apparently predetermined position. Among many violations of the guidelines, EPA had failed to rule out the possibility of bias and other flaws in the ETS studies and also had failed to consider animal studies and other non-epidemiologic data.

"The SAB's report feebly suggested that the panel "had some difficulty in applying the 'Guidelines for Carcinogen Risk Assessment', as they are currently formulated," to the ETS data. Particular attention was given to the report's statement that "[i]f the guidelines for Carcinogen Risk Assessment can be used to cast doubt on a finding that inhalation of tobacco smoke by humans causes an increased risk of lung cancer, the situation suggests a need to revise the guidelines" (SAB Rep. 28). This prompted *one member of the SAB Executive Committee to note that it sounded a little like saying 'if the data doesn't fit the guidelines, the guidelines should be changed.'* Nevertheless, the Committee accepted the panel's Group A designation despite the clear failure of the data to satisfy the Agency's own guidelines.

"Following the Executive Committee meeting, Dr. Lippmann once again spoke to the press about the SAB's conclusions. This time Dr. Lippmann's statements were considerably more restrained than his remarks at the December 1990 press conference. This time he stated that '*occasional, light exposure [to ETS] is not likely to cause any harm*' (United Press International, April 19, 1991). Dr. Lippmann also observed that in his view the risk due to ETS exposure is "probably much less than you took to get here through Washington traffic" (Washington Times, April 19, 1991, p. A-3). On three separate occasions my staff asked Dr. Lippmann, "if one were to apply the guidelines as written could you classify ETS as a Class A known human carcinogen?" On all three occasions, Dr. Lippmann failed to respond to the question. The next day, however, *Dr. Lippmann stated at a meeting outside the glare of media attention that if the guidelines were applied strictly there was no clear mechanistic basis for calling ETS carcinogenic.*

## The Second Draft Risk Assessment

"EPA staff spent the next year and a half attempting to "make a case" against ETS. The revised risk assessment draft was over 600 pages long, finally being issued on the afternoon of June 18, 1992. Incredibly, however, *EPA gave the public just nine working days to comment on it even though the report had doubled in length and a whole new set of flaws had been introduced.* Even the Science Advisory Board panel had only until July 20 to review the revised draft and consider outside comments before the public review meeting.

"The second draft risk assessment was even more curious than the first. As an EPA health scientist who contributed to the draft admitted, the Agency staff had engaged in some "fancy statistical footwork" in the revised risk assessment in order to "fashion [an] indictment" of ETS (*Science*, vol. 257, p. 607 (July 31, 1992)). In the prior draft, EPA's calculations had showed that the epidemiologic studies based on U.S. populations showed no statistically significant association between ETS and lung cancer among nonsmokers. In order to reach a statistically significant result in the first draft, EPA therefore had included in its calculations all of the studies of ETS conducted worldwide to tilt the balance in the favored direction. Both EPA and the SAB rejected out of hand arguments by critics that the risk assessment should have considered only the U.S. studies.

"When EPA staff was revising the risk assessment, however, it was confronted by the Wu-Williams/Blot study, which had been conducted in China and reported a statistically significant negative association between marriage to a smoker and lung cancer among nonsmokers -- the exposure scenario relied upon in the initial risk assessment draft. Inclusion of the Wu-Williams/Blot study in EPA's analysis would have forced EPA to reverse its conclusions about ETS and lung cancer. At the same time, however, EPA had obtained preliminary data from a large U.S. study that, with some massaging, could be used to support its calculations of risk based exclusively on the U.S. studies.

"Accordingly, EPA entirely reversed course and decided in the second draft to disregard the non-U.S. studies. Instead, EPA used the U.S. studies only. *The Agency also adopted an entirely new standard of statistical significance, presumably because the one used in the prior draft would not have yielded the desired results, even with the inclusion of the new, if incomplete, U.S. study.* Only by manipulating the numbers in a manner that violated well-accepted statistical methods was EPA able to claim in the second draft a barely significant association in the U.S. studies.

[Specifically, the revised risk assessment used a 90% confidence interval to judge statistical significance even though (1) a 95% confidence interval had been utilized in all of the underlying studies, (2) a 95% confidence interval is the more accepted measure and (3) EPA had not previously utilized a 90% standard in any previous risk assessment. EPA has never attempted to explain this

departure from previous and accepted scientific practice. One commentator noted that "[t]o get scientifically valid data, there are very strict rules and requirements on how and when you can apply meta-analysis, and virtually all of them were violated in the EPA analysis." Investors' Business Daily, *supra* note 1.

"The new draft also relied on the argument suggested by the SAB that because active smoking had been associated with increases in risk, ETS exposure also must be a risk factor. *The problem with this argument – that ETS is in many respects a very different substance and is encountered at far lower levels – was acknowledged in the revised report.* At the same time, however, its significance seemed to escape those responsible for the report's conclusions.

"Similarly, the second draft risk assessment announced that ETS exposure had been established as a cause of respiratory disease in children. The first draft risk assessment had stated that the data were too inconclusive to draw an inference of causation. No new information became available between the release of the first and second draft risk assessment to support this shift in the Agency's position. Apparently, EPA staff took the SAB's earlier suggestion that it consider 'strengthening' the report's conclusions concerning children as a license to sensationalize further the Agency's claims about ETS.

Although in the past EPA and the scientific community have used a 95% confidence interval as a means of ensuring that study results did not occur by chance, EPA adjusted the confidence interval downward -- to 90% -- in its report on ETS. As James Enstrom, an epidemiology professor at the University of California, Los Angeles, explained, "[t]hat doubles the chance of being wrong."\*\* To put it in lay terms, EPA's statistical maneuvering is the equivalent of moving the goal lines at a football game in order to score more touchdowns. The implications of EPA's willingness to lower scientific standards in selected cases are profoundly troubling. As Michael Gough of Congress's Office of Technology Assessment has pointed out, "[y]ou cannot run science with the government changing the rules all the time."\*\*

\*Investor's Business Daily, *supra* note 1.

\*\**Ibid.*

"The SAB held public hearings on the revised risk assessment on July 21 and 22, 1992, after having denied requests for more time to submit public comments on these and other problems. The panel submitted its report approving the second risk assessment in October. The panel's conclusions make absolutely clear that it was unconcerned with the scientific soundness of the report's underlying rationale. *A brief comparison of the SAB's actions following its first and second review of the risk assessment confirms that the SAB actually disregarded its earlier findings in order to embrace the desired conclusion.*

- "The SAB concluded in its second review that extrapolation from active smoking data could not, after all, serve as the sole or predominant basis for the conclusion that ETS is a Group A carcinogen.

- "The SAB had concluded in its first review that the epidemiologic data were too weak to support the inference that exposure to ETS causes lung cancer in nonsmokers. The SAB reversed its position in its review of the second draft risk assessment once it became clear that active smoking data could not provide an alternative basis for that conclusion.
- "The SAB concluded in its review of the first risk assessment that all studies of ETS and lung cancer conducted worldwide should be included. In the second review, the SAB decided that EPA need only include the U.S. studies. Had the Agency and the SAB adhered to their original decision to use all ETS studies, the meta-analysis would not have shown a statistically significant risk.
- "The SAB nonetheless concluded that the Agency had established that ETS is a Group A carcinogen responsible for approximately 3000 lung cancer cases every year in the United States. In the first review, the SAB had concluded that the data were too uncertain for EPA to attach a specific number to the deaths supposedly attributable to exposure to ETS.

"Put simply, the SAB concluded that ETS is a Group A carcinogen even though neither of the two rationales advanced by EPA staff to justify such classification is scientifically defensible. The first review determined that the spousal smoking studies were too weak to support an inference of causation. The second review concluded that the active smoking data could not be used as an alternative ground. Nonetheless, the SAB decided that the total "weight of evidence" supported a Group A classification.

"Following the SAB's October report, EPA staff rushed to revise and release the final risk assessment. The Agency's haste apparently was motivated in part by the impending change in the Administration. Perhaps of even greater concern to EPA, however, was the release of the Brownson study discussed above. The fact that the largest U.S. case-control study ever conducted reported no statistically significant association between ETS exposure and lung cancer incidence casts further doubt on EPA's claims. *Had the Brownson study been included in EPA's analysis, the Agency's calculations would not have shown a significant risk from ETS even using the Agency's highly suspect statistical methodology.* Rather than face this embarrassment, EPA rushed to release the report without considering the Brownson study on the pretext that 'it had to stop somewhere.'

“Together, EPA and the SAB have undermined the process by which risk assessments ought to be conducted: first, by ignoring the substantial scientific controversy about what the ETS studies actually show; and, second, by conducting the forum where that controversy should have been thoroughly aired as a mere rubber stamp proceeding. As a result, EPA's preparation and review of the risk assessment have given the appearance of a scientific show trial to legitimize a predetermined policy.”

## **Distaste and skepticism**

We were observers before we began writing this public comment. Research into the background of the history of the attempt to list ETS as a human carcinogen has turned us into skeptics. We will take exceptional care in future to assess not only the scientific content and credibility of government-sponsored research; we will also look carefully at the advocacy and activist “credentials” of grant recipients and spokespersons for government-issued “facts.”

Mr. Repace casts a rather unnecessary and unpleasant aspersion on p 203 of the transcript. “The North Carolina court, which vacated the ETS risk assessment, the judge has no apparent scientific credentials that we are aware of.” Ironically, Mr. Repace's comments sent us to a full transcript of Judge Osteen's decision regarding the EPA assessment of ETS as a human carcinogen. We were gratified to find that this decision pointed out several of the astounding errors in methodology that we found in reviewing the material from NTP. The decision also revealed a process that appears to have been corrupted by EPA's *a priori* assumption that ETS is a carcinogen and detailed so ably by Mr. Bliley in his Congressional testimony. We remind readers that Mr. Bliley was largely responsible for the release of millions of pages of tobacco industry documents.

We found it odd that Mr. Repace chose Judge William Osteen as the target for his *ad hominem* comments. Judge Osteen is a respected jurist who was responsible for the decision granting the US Food and Drug Administration jurisdiction over cigarettes. This is hardly evidence of bias toward the tobacco industry. Osteen's court uses the services of independent specialists. Judge Osteen does not need to be a scientific expert. He hires verifiably independent experts to advise his court. Perhaps it would be a good idea if the USEPA and the NTP did the same.

## **8. CONCLUSION**

The distorted selection of studies used for meta-analysis, the midstream alteration of confidence interval, the past record of rushing adverse decisions about the putative ‘danger’ of ETS -- all are desperate attempts to ‘reach the verdict before the trial’; a concept stated quite clearly by the delightful mathematician Lewis Carroll in his story of *Alice in Wonderland*.

The contention that ETS is a health hazard of any kind is based almost entirely on argument by analogy -- using data based on lung cancer and direct smoking. It is an argument that simply does not hold up under scrutiny. We conclude that the Rule of Occam's Razor applies -- the simplest answer is the correct one: *ETS is simply NOT a carcinogen at any reasonable level of human exposure.*

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